The Effect of M694V Mutation on Clinical Presentation and Acute Phase Response in Children with Familial Mediterranean Fever: Single Center Experience in Western Turkey

Ailevi Akdeniz Ateşi Olan Çocuklarda M694V Mutasyonunun Klinik Görünüm ve Akut Faz Yanıtına Etkisi: Türkiye'nin Batısında Tek Merkez Deneyimi

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ABSTRACT Objective: The aim of this study was to investigate the phenotype-genotype correlation and the relationship between clinical severity score and acute phase response in children with familial Mediterranean fever (FMF) in Western Turkey. **Material and Methods:** The medical records of 87 FMF children (mean age: 11.1 ± 3.6 years; range: 3-20 years; mean age at diagnosis: 8.3 ± 3.5 years; mean follow up: 31.2 ± 27.7 months; female: 55.2%) mutations on MEFV gene were retrospectively reviewed. We used Tel Hashomer diagnostic criteria and severity score. Correlations between white blood cell (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) during attack-period as well as clinical severity scores were investigated. The patients were grouped according to one or two alleled mutations and the presence of the M694V mutation. Clinical parameters and WBC, CRP and ESR levels were compared among the groups. **Results:** M694V homozygosity was found in 22 patients (25.3%). Amyloidosis was seen in six patients (6.9%). All of them had M694V homozygote mutation. The measured WBC (r= 0.294; p: 0.006), CRP (r= 0.720; p< 0.001) and ESR (r= 0.716; p< 0.001) values were correlated with clinical severity score. The presence of two mutated alleles or M694V homozygosity was associated with a higher clinical severity score, higher levels of WBC, CRP and ESR as well as higher risk of amyloidosis compared to the others (p< 0.05). **Conclusion:** M694V homozygote genotype shows higher acute phase response during attack-period and severe clinical course in children with FMF in Western region of Turkey.

Key Words: Familial Mediterranean Fever; acute-phase reaction; genotype; child; Turkey

ÖZET Amaç: Bu çalışmanın amacı Türkiye'nin batısındaki ailesel Akdeniz ateşi (AAA) tanılı çocuklarda fenotip-genotip korelasyonunu ve klinik şiddet skoru ile akut faz yanıtı arasındaki ilişkiyi araştırmaktı. **Gereç ve Yöntemler:** MEFV geninde mutasyon saptanan AAA tanılı 87 çocuğun (ortalama yaş: 11.1 ± 3.6 yıl; aralık: 3-20 yıl; tanı anındaki ortalama yaş: 8.3 ± 3.5 yıl; ortalama izlem süresi: 31.2 ± 27.7 ay; kız: %55.2) tıbbi kayıtları geriye dönük olarak gözden geçirildi. Tel Hashomer tanı kriterleri ve şiddet skoru kullanıldı. Atak sırasındaki beyaz küre sayısı (BKS), C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESH) ile klinik şiddet skoru arasındaki korelasyonlar araştırıldı. Hastalar bir veya iki alelde mutasyon olma durumu ve M694V mutasyonunun varlığına göre gruplandırıldılar. Gruplar arasında klinik parametreler ile BKS, CRP ve ESH düzeyleri karşılaştırıldı. **Bulgular:** Yirmi iki (%25.3) hastada M694V homozigotluğu bulundu. Altı hastada (%6.9) amiloidoz gelişti. Bunların tamamında M694V homozigot mutasyonu vardı. Ölçülen BKS (r= 0.294; p: 0.006), CRP (r= 0.720; p<0.001) ve ESH (r= 0.716; p< 0.001) değerleri klinik şiddet skoru ile bağıntılıydı. İki alelde mutasyon varlığı veya M694V homozigotluğu daha yüksek klinik şiddet skoru , daha yüksek seviyede BKS, CRP ve ESH düzeyleri ile daha fazla amiloidoz riskiyle ilişkiliydi (p< 0.05). **Sonuç:** Türkiye'nin batısında M694V homozigot genotipine sahip AAA'li çocuklar atak döneminde daha yüksek akut faz yanıtı ve ağır klinik gidiş göstermektedirler.

Anahtar Kelimeler: Ailesel Akdeniz Ateşi; akut faz yanıtı; genotip; çocuk; Türkiye

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent self-limited episodes of fever and serosal inflammation accompanied by a marked acute-phase response. It affects primarily people of Jewish, Turkish, Arab, and Armenian ancestries. The most devastating complication of FMF is amyloidosis, leading to chronic renal failure. The frequency is higher in non-Ashkenazi Jews and Anatolian Turks. The FMF gene called MEFV was mapped to the short arm of chromosome 16. The five most common mutations are M694V, M680I, M694I, E148Q, and V726A. Although phenotype-genotype relationship is not well established, several researchers have observed more severe disease expression and increased susceptibility to amyloidosis in patients with M694V mutation. However, studies implicated that environmental factors affect the risk of developing amyloidosis.[1-3]

The purpose of this study was to investigate the phenotype-genotype correlation and the predictors of prognosis in children with FMF in the Western region of Turkey assessed by acute phase response during attack-period and clinical severity score.

MATERIAL AND METHODS

We retrospectively reviewed the medical records of 87 children with FMF who were diagnosed between January 1996 and June 2006 and followed up for at least one year in the Pediatric Nephrology Unit of Tepecik Training and Research Hospital, Izmir, Turkey. The origin of all patients was Turkish and they were living in Western region of Turkey. The diagnosis of FMF was made based on Tel Hashomer diagnostic criteria.[4]

The measured white blood cell count (WBC) (/mm^3), levels of C-reactive protein (CRP) (by nephelometric metod; mg/dl) and erythrocyte sedimentation rate (ESR) (by Westergreen method; mm/h) during attack-period were recorded. Genomic DNA was extracted from patients by obtaining 5 ml of whole blood using the conventional phenol-chloroform extraction method. A reverse hybridization assay (FMF StripAssay, ViennaLab Labordiagnostika, Vienna, Austria) was used for the detection of the 12 most frequent MEFV mutations located in exon 2, p.E148Q (c.442G>C); exon 3, p.P369S (c.1105C>T); exon 5, p.F479L (c.1437C>G); and exon 10, p.M680I (c.2040G>C), p.M680I (c.2040G>A), I692del (c.2076>2078del), p.M694V (c.2080A>G), pM694I (c.2082G>A), p.K695R (c.2084A>G), p.V726A (c.2177T>C), p.A744S (c.2230G>T), and p.R761H (c.2282G>A). Data were collected from the medical charts and, if necessary by interview. Response to colchicine treatment was evaluated as complete (attack free), incomplete (decline >50% in the frequency of attacks) and unresponsive, according to clinical condition. The severity score of the disease was calculated based on the Tel Hashomer Severity Score,[5] including the parameters of age of onset (<5 years: 3, 5-10 years: 2, 10-20 years: 1, >20 years: 0), frequency of attacks (>2 per month: 3, 1-2 per month: 2, <1 per month: 1), colchicine dosage to control attacks (non-responder: 4, 2 mg/day: 3, 1.5 mg/day: 2, 1 mg/day: 1), arthritis (protracted arthritis: 3, presence of acute joints: 2), erysipelas-like erythema (2 points), amyloidosis (3 points) and phenotype II (4 points). Patients presenting with amyloidosis before the onset of clinical symptoms of FMF were designated as having phenotype II. In patients with persistent proteinuria or nephrotic syndrome, a kidney biopsy was done. The histological diagnosis of amyloidosis was confirmed by the presence of amyloid deposits on Congo red staining under polarized light microscopy.

Data were analyzed using SPSS 13.0 (Chicago, IL, USA) statistical program. Continous variables measured as ratios were assumed to be normally distributed and expressed as mean±SD (standart deviation). Median and interquartile range (IQR) were used for the other variables which were expressed as count data and were not normally distributed. For the variables which were normally distributed, Student t-test (between two independent groups), and one-way ANOVA (among more than two groups) were used to test equality of the means of the different groups. Mann-Whitney U test and Kruskal–Wallis test are nonparametric alternatives of Student t-test and ANOVA, respectively. They do not rely on an assumption of normality. For other variables, Mann-Whitney U and Kruskal-Wallis tests were used to evaluate the differences between groups. We compared categorical data with Chi-

square test. The correlations between WBC, CRP, ESR and severity score were analyzed by Spearman's correlation method. A p-value less than 0.05 was considered as significant.

This study was approved by the hospital ethics committee.

RESULTS

The diagnosis of 87 patients (48 girls, 39 boys) with clinically defined FMF was confirmed by mutation analysis. The mean age of patients was 11.1±3.6 years (range: 3-20; median age: 11 years). Mean follow up duration was 31.2±27.7 months (range: 12-128; median follow up: 24). All subjects were phenotype I patients. Nine patients (10.3%) had proteinuria. Renal biopsy revealed amyloidosis in six patients (6.9%). Remaining three patients were diagnosed with IgA nephropathy. Table 1 summarizes demographic and phenotypic features of the study group.

In the genetic analyses, the number of homozygotes, heterozygotes and compound heterozygotes were 22 (25.3%), 18 (20.7%) and 13 (14.3%), respectively. Homozygosity for M694V was the most frequent mutation (22 patients, 25.3%). The mean severity score of homozygotes for M694V mutation was 10.5±2.6. Higher WBC, CRP and ESR levels were found during attack-period in M694V homozygote or compound heterozygote genotypes compared to the others (Table 2).

WBC (r= 0.294; P= 0.006), CRP (r= 0.720; P<0.001) and ESR (r= 0.716; P<0.001) levels were significantly correlated with severity score in FMF patients (Figures 1-3).

Patients were divided into two groups according to the number of mutated alleles (Table 3).

Presence of two mutated alleles was associated with a younger age at onset (P=0.005), more frequent arthritis (P=0.007), higher number of attacks

TABLE 1: The demographic and phenotypic features of FMF patients (n=87)

Features	
Sex	
Male (n, %)	39 (44.8)
Female (n, %)	48 (55.2)
Age at onset, years [(Mean±SD (range)]	5.6±2.6 (1.5-12)
Age at diagnosis, years [(Mean±SD (range)]	8.3±3.5 (2-17)
Time interval between disease onset and diagnosis, years [(Mean±SD (range)]	2.7±2.6 (0.6-13)
Abdominal pain (n, %)	85 (97.7)
Fever (n, %)	63 (72.4)
Arthritis (n, %)	51 (58.6)
Erysipelas-like erythema (n, %)	15 (17.2)
Myalgia (n, %)	7 (8)
Chest pain (n, %)	5 (5.7)
No. of attacks per year before treatment, median (IQR)	12 (44)
No. of attacks per year after treatment, median (IQR)	2 (50)
Severity score, median (IQR)	7 (14)
Response to colchicine	
Complete (n, %)	34 (39.1)
Incomplete (n, %)	36 (41.4)
Non-responsive (n, %)	17 (19.5)
Proteinuria (n, %)	9 (10.3)
Amyloidosis (n, %)	6 (6.9)
Underwent surgery (n, %)	8 (9.2)
Mortality (n, %)	3 (3.4)
Family history of FMF (n, %)	32 (36.8)

SD: Standart deviation; IQR: Interquartile range, FMF: Familial Mediterranean fever.

TABLE 2: Distribution of severity scores and levels of WBC, CRP and ESR according to genotype in FMF patients.

Mutation	n (%)	Severity score Mean±SD (n)	WBC Mean±SD (/mm³)	CRP Mean±SD (mg/dl)	ESR Mean±SD (mm/h)
Met694Val-Met694Val	22 (25.3)	10.5±2.6	13154.5±9306.9	4.1±1.6	49.8±11.5
Met694Val-?	18 (20.7)	7.5±2.3	11710.5±5977.5	3.6±2.4	41.0±17.7
E148Q-?	11 (12.6)	4.8±1.5	6659.0±968.7	0.5±0.1	19.7±13.0
Val726Ala-?	6 (6.9)	6.3±1.7	13000.0±7030.5	1.2±0.7	24.5±6.8
Met694Val- E148Q	4 (4.6)	7.5±0.5	20000.0±1169.1	2.6±1.4	54.2±9.6
Met694Val- Met680Val	3 (3.4)	9.0±2.6	20466.6±12371.4	3.9±1.4	50.6±4.9
Met694Val- Val726Ala	3 (3.4)	8.6±2.0	19866.6±12200.5	5.0±2.4	53.3±12.7
Met680Val-R761H	3 (3.4)	6.6±3.0	7466.6±1803.6	0.7±0.0	37.6±9.2
Met694Val-R761H	2 (2.3)	6.5±0.7	7800.0±424.2	2.0±0.9	14.0±2.0
Val726Ala- Val726Ala	2 (2.3)	5.5±2.1	7775.0±1308.1	0.5±0.2	26.0±14.1
R314R-?	2 (2.3)	3.5±0.7	16500.0±6363.9	0.5±0.2	20.0±2.0
Met694Val-P369S	1 (1.1)	5	24000	2.1	42
Met680Val-E148Q	1 (1.1)	5	15000	2.4	38
Val726Ala-Met680I	1 (1.1)	5	8450.0	0.3	22
Met680I-Met694I	1 (1.1)	7	7800	0.8	17
A744S-A744S	1 (1.1)	5	9200	0.4	21
F479L-?	1 (1.1)	5	8450	0.4	12
A744S-?	1 (1.1)	5	6000	0.5	18
R671H-?	1 (1.1)	5	9800	0.5	20
P369S-?	1 (1.1)	4	5500	0.5	21
K695R-?	1 (1.1)	5	7800	0.6	19
R761H-?	1 (1.1)	5	8450	0.4	21

SD: Standard deviation, WBC: white blood cell count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

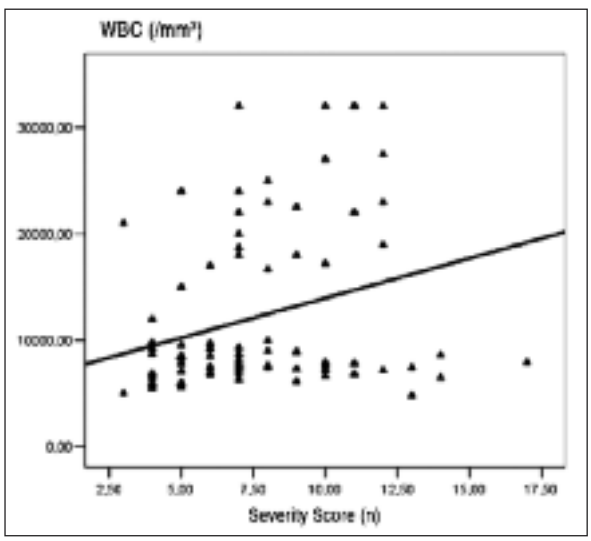

FIGURE 1: The positive correlation between white blood cell (WBC) level and Tel Hashomer Severity Score (r= 0.294; P= 0.006).

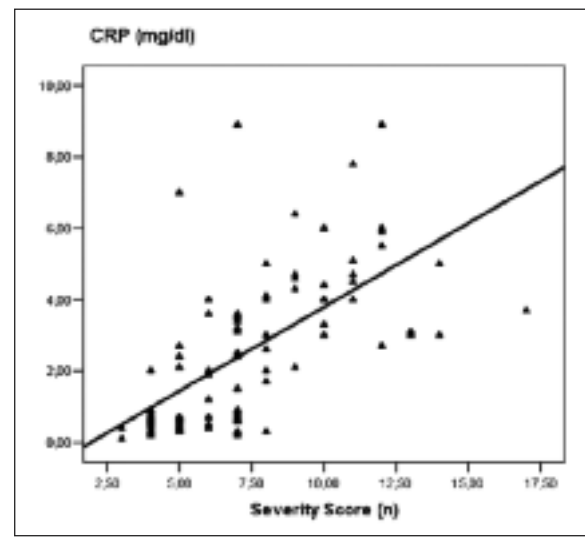

FIGURE 2: The positive correlation between C-reactive protein (CRP) level and Tel Hashomer Severity Score (r= 0.720; P<0.001).

per year before (P<0.001) and after (P<0.001) treatment, higher severity scores (P<0.001), lower rate of response to colchicine treatment (P<0.001), more frequent of proteinuria (P=0.002) and amyloidosis (P=0.013), as well as higher WBC (P=0.030), ESR (P<0.001) and CRP (P=0.003) levels.

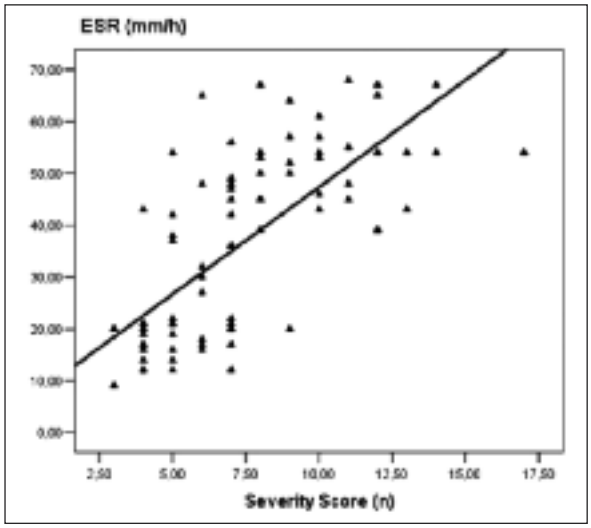

FIGURE 3: The positive correlation between erythrocyte sedimentation rate (ESR) and Tel Hashomer Severity Score (r= 0.716; P<0.001).

Our patients were also classified into three groups according to mutations: Met694Val-Met694Val (group 1), Met694Val-other (group 2, including Met694Val heterozygote or compound heterozygote) and other-other (group 3) (Table 4).

Groups 1 and 2 were associated with younger age at onset (P<0.001) and higher WBC (P=0.012), ESR (P<0.001) and CRP (P<0.001) levels. The shortest interval between disease onset and diagnosis was found in Group 2 (P<0.001). Arthritis (P<0.001), erysipelas-like erythema (P=0.003), proteinuria (P=0.001) and amyloidosis (P<0.001) were more frequent in Group 1. Significant differences were detected between the groups with regard to the rate of response to colchicine treatment, number of attacks per year before and after treatment

TABLE 3: Comparison of demographic, clinical and laboratory parameters in the patients with FMF with respect to one or two mutated alleles.

Parameter	One mutated allele n=43	Two mutated alleles n=44	P
Female, n (%)	25 (58.1)	23 (52.3)	0.584[b]
Age at onset (years)	6.4±2.6	4.8±2.5	0.005[a]
Age at diagnosis (years)	8.6±3.4	8.0±3.6	0.402[a]
Time interval between age at onset and diagnosis (years)	2.2±2.4	3.2±2.7	0.084[a]
Abdominal pain, n (%)	43 (100)	42 (95.5)	0.160[b]
Fever, n (%)	30 (69.8)	33 (75)	0.587[b]
Arthritis, n (%)	19 (44.1)	32 (72.7)	0.007[b]
Erysipalas-like erythema, n (%)	5 (11.6)	10 (22.7)	0.173[b]
Myalgia, n (%)	1 (2.3)	6 (13.6)	0.054[b]
Chest pain, n (%)	3 (7)	2 (4.5)	0.628[b]
No. attacks per year before treatment, median (IQR)	6 (7)	16.5 (15.5)	<0.001[b]
No. attacks per year after treatment, median (IQR)	0 (2.5)	11 (16)	<0.001[b]
Severity score, median (IQR)	5 (3)	8 (4)	<0.001[b]
Response to colchicine treatment, n (%)	41 (95.3)	29 (65.9)	<0.001[b]
Proteinuria, n (%)	0 (0)	16 (36.4)	0.002[b]
Amyloidosis, n (%)	0 (0)	9 (20.5)	0.013[b]
Mortality, n (%)	0 (0)	3 (6.8)	0.083[b]
Family history of FMF, n (%)	17 (39.5)	20 (45.5)	0.436[b]
WBC (/mm^3), mean±SD	10256.7±5480.4	13851±9215	0.030[a]
ESR (mm/hour), mean±SD	29.4±16.5	44.1±15.6	<0.001[a]
CRP (mg/dl), mean±SD	1.9±	3.2±1.9	0.003[a]

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein; IQR: Interquartile range; SD: Standard deviation.
[a] t-test; [b] Mann-Whitney U test.

TABLE 4: Comparison of demographic, clinical and laboratory parameters in the patients with FMF with respect to Met694Val mutation.

	Group 1 Met694Val- Met694Val	Group 2 Met694Val- other	Group 3 Other-other	
Parameter	**n=22**	**n=31**	**n=34**	**P**
Female/male	10/12	17/14	21/13	0.491[b]
Age at onset (years), mean±SD	4.2±2.1	5.0±2.3	7.0±2.6	<0.001[a1]
Age at diagnosis (years), mean±SD	8.2±3.7	8.2±4.1	8.5±2.8	0.941[a]
Time interval between disease onset and diagnosis (years), mean±SD	2.4±1.4	3.0±2.1	2.2±1.4	<0.001[a2]
Abdominal pain, n (%)	22 (100)	29 (93.5)	34 (100)	0.161[b]
Fever, n (%)	17 (77.3)	21 (67.7)	25 (73.5)	0.736[b]
Arthritis, n (%)	18 (81.8)	24 (77.4)	9 (26.5)	<0.001[b3]
Erysipelas-like erythema, n (%)	9 (40.9)	4 (12.9)	2 (5.9)	0.003[b3]
Myalgia, n (%)	5 (22.7)	0	2 (5.9)	0.010[b]
Chest pain, n (%)	1 (4.5)	4 (12.9)	0	0.082[b]
No. attacks per year before treatment, median (IQR)	23 (12)	12 (16)	6 (4)	<0.001[b4]
No. attacks per year after treatment, median (IQR)	14.5 (12)	4 (10)	0 (0)	<0.001[b4]
Severity score, median (IQR)	10.5 (3)	7 (2)	5 (2)	<0.001[b4]
Response to colchicine treatment, n (%)	10 (45.4)	27 (87.0)	33 (97.0)	<0.001[b4]
Proteinuria, n (%)	7 (31.8)	2 (6.4)	0	0.001[b3]
Amyloidosis, n (%)	6 (27.2)	0	0	<0.001[b3]
Family history of FMF, n (%)	9 (40.9)	12 (38.7)	11 (32.3)	0.615[b]
WBC (/mm^3), mean±SD	13154.5±5480.4	14560.9±8589.0	9108.0±4422.1	0.012[a1]
ESR (mm/hour), mean±SD	49.8±11.5	43.1±17.1	22.8±10.3	<0.001[a1]
CRP (mg/dl), mean±SD	4.1±1.6	3.4±2.2	0.8±0.7	<0.001[a1]

IQR: Interquartile range; SD: Standard deviation, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.

[a] ANOVA

[b] Kruskal-Wallis test

[1] Group 1 and 2 are significantly different from Group 3

[2] Group 2 is significantly different from Group 1 and 3

[3] Group 1 is significantly different from Group 2 and 3

[4] Three groups are significantly different from each other

and severity score. The greatest number of attacks per year before and after treatment were found in Group 1 whereas the smallest number of attacks before and after treatment were found in Group 3 (P<0.001). Group 1 showed the highest severity score and the lowest rate of response to colchicine treatment whereas Group 3 experienced the lowest severity score and the highest rate of response to colchicine treatment (P<0.001).

DISCUSSION

This single-center study from Western region of Turkey investigated 87 children with FMF in whom the MEFV alleles had been identified to determine the phenotype-genotype association and risk factors for amyloidosis. Although a male predominance has been reported in Arab, Armenian, and Jewish and Turkish patients, we observed a slight female superiority (male:female ratio of 1:1.2).[2,6-10] In addition, the age of the disease onset and the diagnosis were found to be smaller compared to large studies and similar to a study from Turkey.[2,9,11] In our series, abdominal pain was the most common feature (97.7%), followed by fever (72.4%) and joint involvement (58.6%). These findings were similar to the results of other studies on Turkish and Jewish societies.[2,8,9,11,12] The rates of erysipelas-like erythema (17.2%), myalgia (8%) and pleuritis (5.7%) were lo-

wer than Turkish FMF Study Group records but similar to the report from Central Anatolia.[2,11] The rate of erysipelas-like erythema in our study was higher than Arabs and Armenians.[13,14]

The five most common mutations are M694V, M680I, M694I, E148Q, and V726A.[1,3] The Met694Val mutation was the most common one (60.9%) of the tested alleles in our study group, as reported in other studies from Turkey.[1,2,9,11,12] Interestingly, the second most frequent mutation was E148Q (18.4%) in the present study.

It is well known that increased acute phase response during attacks is a characteristic finding of FMF. Moreover, FMF patients may also show higher acute phase response in their attack-free periods due to ongoing subclinical inflammation.[1,3] Tunca et al. reported higher CRP and serum amyloid A protein (SAA) levels in patients with FMF and their healthy first-degree relatives.[15] Duzova et al. found that SAA (not CRP, ESR, fibrinogen or ferritin) was the best marker of ongoing subclinical inflammation in FMF patients.[16] Korkmaz et al. showed a marked acute phase response during FMF attacks and high CRP levels in all attacks.[17] On the other hand, a study on limited number of patients from the Aegean region by Türkmen et al., reported that homozygosity for M694V did not affect acute phase markers.[18] In the present study, we observed that high levels of WBC, CRP and ESR during the attack-period were associated with high severity scores. In the presence of M694V genotype, high WBC, CRP and ESR levels were measured during the attack-period. These results may support the severity of M694V mutation on laboratory basis. Unfortunately, we could not measure SAA level of the patients due to nonavailability. To our knowledge, this is the first study that investigates the relationship between acute phase proteins during attack-period and clinical severity score in patients with FMF.

In our series, two mutated alleles were M694V homozygotes (25.3%), M694V compound heterozygotes (14.9%), and homozygotes for other alleles and other compound heterozygote genotypes (10.3%). The findings of the present study confirmed that any two mutations, as compared with one mutation, correlated with more severe disease.[19] We found that earlier age, higher attack rate before and after treatment, higher severity score, low response rate to colchicine treatment, higher rate of proteinuria and amyloidosis as well as higher WBC, CRP and ESR levels were associated with the presence of two mutated alleles. The significantly higher acute-phase response in attack period were detected in patients with two mutated alleles compared to those with one mutated allele. It is clearly seen that increased clinical and laboratory severity of the two mutated alleles which included M694V mutation most of the time, was related to the presence of M694V genotype in the present study.

The most devastating complication of FMF is amyloidosis, which affects the kidneys leading to chronic renal failure. The prevalence of amyloidosis differs among various ethnic groups.[1,3] Amyloidosis was reported as 2% in Arabs, 27.6% in Sephardic Jews, 24% in Armenians and 12.9% in Turks.[1,2,8,13] In the present study, amyloidosis was found in 6.9% of the patients.

The genotype-phenotype correlation is not well established.[1] Several studies from different countries as well as different regions of Turkey have emphasized that M694V homozygous genotype have a more severe form of disease manifested by an earlier age of onset, higher frequency of attacks, higher prevalence of arthritis and pleurisy, higher frequency of amyloidosis and higher severity scores compared to the other genotypes.[2,11,20-25] On the contrary, some studies showed that the presence of M694V mutation was not found to be associated with a severe form of the disease or the development of amyloidosis.[2,9,11] Recently, in a large cohort study from the Aegean region of Turkey, the M694V homozygous mutation was found most frequently in a definitive FMF group, based on Tel-Hashomer criteria.[26] In Western region of Turkey, we found that M694V homozygote mutation was associated with a severe clinical course whereas E148Q mutation was associated with a preferable clinical course. Earlier age at onset of disease, higher frequencies of arthritis, erysipelas-like erythema and myalgia, higher attack rate and severity score, low response rate to colchicine treatment,

and higher levels of WBC, CRP and ESR during attack-period were associated with the presence of M694V mutation in our study. The genotypes of all patients with proteinuria and amyloidosis included M694V mutation at least in one allele, and all of the patients with amyloidosis had M694V homozygote genotype. Interestingly, the time interval between disease onset and diagnosis in children with Met694Val-other mutation (Group 2) was significantly longer than the others. Furthermore, although insignificant, the shortest interval was found in non-Met694Val genotypes. It is likely that the later onset of the disease in these children could be associated with the earlier diagnosis due to easier expression of the complaints in the older age.

To our knowledge, this study highlights some important features. Firstly, this is the first study which assessed the children with FMF living in Western region of Turkey. Secondly, this report is the first that showed a positive correlation between the level of acute phase response in attack-period and the severity of clinical score.

CONCLUSION

This study showed a phenotype-genotype correlation in FMF patients living in Western region of Turkey. In conclusion, we have revealed that M694V homozygosity is associated with a more severe course and development of amyloidosis when compared to other common genotypes in our region.

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