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ORIGINAL ARTICLE

MEFV gene mutations in children with Henoch–Schönlein purpura and their correlations—do mutations matter?

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Abstract

Objective To explore the frequency of *MEFV* gene mutations in children with Henoch–Schönlein purpura who had no prior familial Mediterranean fever diagnosis and to evaluate the association of *MEFV* mutations with the clinical and laboratory features of Henoch–Schönlein purpura.

Methods Data of 1120 patients diagnosed with Henoch–Schönlein purpura were reviewed retrospectively. The spectrum and degree of organ involvement and acute phase reactant levels were documented for each patient. Blood for *MEFV* gene mutation analysis was obtained either at the time of the Henoch–Schönlein purpura diagnosis or during follow-up visits. Pathological specimens of patients who underwent biopsy (renal/skin) were evaluated with special consideration for immunofluorescent examinations.

Results Two hundred and thirty-eight (21.3%) patients were found to have one of the *MEFV* mutations in which exon 10 mutations were the most common (16.7%). Abdominal pain, joint involvement, scrotal involvement, and relapse were more frequent, and acute-phase reactant levels were significantly high in patients with *MEFV* mutations. More severe characteristics were observed in the presence of homozygous exon 10 mutations. There was no significant association between exon 2 variants and clinical course of Henoch–Schönlein purpura. Patients carrying *MEFV* mutations did not have significantly higher levels of IgA deposits in the biopsy materials.

Conclusion Henoch–Schönlein purpura in patients with homozygous exon 10 *MEFV* mutations seems to be more severe than that in patients carrying other mutations. In patients with exon 10 *MEFV* mutations, Henoch–Schönlein purpura might be considered as an associated presentation of familial Mediterranean fever rather than a separate clinical entity.

Key points
- *p.M694V mutation is more common in Henoch–Schönlein purpura than in the general population.*
- *p.E148Q variants have no impact on clinical symptoms and laboratory findings in Henoch–Schönlein purpura patients.*
- *The majority of Henoch–Schönlein purpura patients with familial Mediterranean fever have no IgA deposits.*
- *Henoch–Schönlein purpura in familial Mediterranean fever patients may be considered as an integral clinical feature of familial Mediterranean fever.*

Keywords Children · Familial Mediterranean fever · Henoch–Schönlein purpura · *MEFV* gene

Introduction

Henoch–Schönlein purpura (HSP) is the most common systemic vasculitis in childhood and was renamed as IgA vasculitis in recent years. It is characterized by the presence of immunoglobulin A1 (IgA1)-dominant immune deposits in the small vessels. Palpable purpura, abdominal pain, arthritis or arthralgia, and nephritis are the main findings [1, 2]. The etiology of HSP is not clear; both genetic and environmental factors are thought to play role in the disease development [3]. Several studies addressed the issue whether *MEFV* mutations were related to susceptibility to HSP and outcome [4–7]. Familial Mediterranean fever (FMF) is the most common monogenic auto-inflammatory disease affecting mainly the Mediterranean population which is caused by mutations in the *MEFV* gene. Self-limited inflammatory attacks of fever

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and polyserositis along with elevated acute-phase reactants are characteristic for the disease [8]. The co-occurrence of HSP and FMF has been explained by the hypothesis that *MEFV* gene mutations cause an uncontrolled inflammatory response via the pyrine protein which has role in suppressing the inflammatory pathways [5]. As distinct from, it is recently speculated that cutaneous vasculitis should be considered as atypical manifestation of FMF, rather than a comorbidity [9].

The purpose of this study is to investigate the frequency and types of *MEFV* gene mutations and variants in children with HSP who were followed up at a tertiary center in Turkey and to assess the impact of the *MEFV* gene mutations and variants on clinical and laboratory findings. In addition, we divided the patients with renal or skin biopsy into two groups, *MEFV* gene mutation positive and negative, and compared them based on the existence of IgA deposits in direct immunofluorescence (DIF) evaluation.

Materials and methods

Patients

A total of 1120 children diagnosed with HSP at Dr. Sami Ulus Children's Hospital Department of Nephrology and Rheumatology between January 2001 and November 2016 were included in the study. HSP diagnosis was made according to the criteria of the European League Against Rheumatism [10]. Patients with at least 1-year follow-up were included in the study. Patients with diagnosis of FMF prior to the onset of HSP were excluded. Data regarding clinical and laboratory characteristics of patients were gathered from hospital records. Age at diagnosis, gender, duration of follow-up, symptoms, and acute-phase reactants including erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels were documented. Blood samples for DNA analysis were obtained from all patients either at the time of diagnosis of HSP or during follow-up visits.

Renal biopsy was performed when patients presented with nephritic syndrome, nephrotic range proteinuria, persistent proteinuria of 4–40 mg/m^2/h for more than 3 months and/or renal impairment. All biopsies were performed prior to the initiation of drug therapy. Also in cases with atypical rash, skin biopsy was performed. Six patients were excluded from the study, because the skin biopsy samples did not include a middle-sized artery.

Patients were first divided into two main groups as *MEFV* mutation positive and negative. A detailed grouping according to the type of mutations was also made as exon 10 homozygous, exon 10 heterozygous, exon 10 and exon 2 compound heterozygous, and exon 2 or 3 variants. The study was approved by the Institutional Ethics Committee (E-18-2012).

Detection of the MEFV gene mutations

Twelve common *MEFV* mutations (p.E148Q in exon 2, p.P369S in exon 3, p.F479L in exon 5, and p.M694V, p.M694I, p.M680I (G/C), p.M680I (G/A), p.V726, p.I692del, p.K695R, p.A744S, and p.R761H in exon 10) were investigated simultaneously by a reverse-hybridization assay (FMF StripAssay; ViennaLab, Gaudenzdorfer Gürtel, Vienna, Austria; http://www.viennalab.com/) based on sequence-specific hybridization following amplification by PCR. DNA was isolated from anticoagulated venous blood samples using standard techniques, *MEFV* sequences were in vitro amplified and biotin-labeled simultaneously in a single (multiplex) amplification reaction. Finally, the amplification products were selectively hybridized to a test strip, which contains oligonucleotide probes (wild type- and mutant-specific) immobilized as parallel lines. Bound biotinylated sequences were detected using streptavidin-alkaline phosphatase and color substrates.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 16.0 for Windows (South Wacker Drive, Chicago, IL, USA) was used for statistical analysis. Shapiro–Wilk test was used to test distribution of normality. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages. Student's *t* test and Mann–Whitney *U* test were used where appropriate to compare continuous variables. Chi-square test was used to compare categorical variables. A p value less than 0.05 was considered statistically significant.

Results

The study group consisted of 1120 patients (646 boys and 474 girls) with HSP. Mean age at the time of diagnosis was 7.4 ± 3.4 (range 2 to 18 years). The mean follow-up period of patients was 8.4 ± 3.5 years. Purpura was the consistent finding in all patients at first admission. Overall, arthritis or arthralgia occurred in 475 patients (42.4%), while gastrointestinal involvement in 437 (39%), renal involvement in 414 (37%), and scrotal involvement in 60 (5.4%). Thirty-eight patients showed recurrence of HSP.

At least one *MEFV* mutation or polymorphism was detected in 238 (21.2%) of 1120 HSP patients. Forty of them (3.5%) were homozygous, and 178 (15.6%) were heterozygous for one mutation, while 20 patients (1.7%) were compound heterozygotes (Table 1). In all three groups, the majority of the patients (126 patients) had p.M694V mutation in at least one allele, which makes 52.9% of mutation-positive patients and

Table 1 Distribution of *MEFV* genotypes in 238 children with Henoch–Schönlein purpura

Genotype	Number	Percentage
Mutation (−)	882	78.7
Heterozygous for one mutation	178	15.68
p.M694V/−	90	8.03
p.M680I/−	21	1.87
p.E148Q/−	35	3.12
p.V726A/−	11	0.98
p.M694I/−	7	0.62
p.K695R/−	4	0.35
p.P369S/−	8	0.71
Homozygous for one mutation	40	3.53
p.M694V/p.M694V	19	1.69
p.M680I/p.M680I	5	0.44
p.V726A/p.V726A	3	0.26
p.E148Q/p.E148Q	6	0.53
p. M694I/M694I	4	0.35
p.P369S/P369S	3	0.26
Compound heterozygous for two mutations	20	1.76
p.M694V/p. M680I	7	0.62
p.M694V/p.V726A	6	0.53
p.M694V/p.E148Q	4	0.35
p.M680I/p.E148Q	3	0.26

11.2% of 1120 HSP patients, respectively. A detailed description of genotype distribution is presented in Table 1.

Clinical and laboratory characteristics of the patients with and without *MEFV* gene mutations are summarized in Table 2. Age and sex distributions were found to be similar between both groups. The rates of arthritis, abdominal pain, scrotal involvement, relapse rates, and level of acute-phase reactants were higher in patients with *MEFV* mutations than in patients without ($p < 0.001$) (Table 2). In the long-term follow-up, only 5 patients had end-stage renal failure, and one of them had *MEFV* gene mutation.

Table 2 Comparison of clinical and laboratory features of Henoch–Schönlein purpura patients

	Patients without *MEFV* mutations ($n = 882$)	Patients with *MEFV* mutations ($n = 238$)	p
Age, years	8.2 ± 3.54	8.1 ± 3.44	0.572
Sex, *n* (%)			
Male	504 (57.1%)	142 (59.7%)	0.485
Female	378 (42.9%)	96 (40.3%)	
Arthritis	345 (39.1%)	129 (54.2%)	*< 0.001*
Abdominal pain	282 (32%)	156 (65.5%)	*< 0.001*
Severe GIS involvement	213 (24.1%)	60 (25.2%)	0.735
Scrotal involvement	33 (3.7%)	27 (11.3%)	*< 0.001*
Renal involvement	324 (36.7%)	87 (36.6%)	0.959
Elevated ESH	606 (75.1%)	201 (84.5%)	*< 0.001*
Elevated CRP	447 (50.7%)	187 (78.6%)	*< 0.001*
Relapse	17 (1.9%)	21 (8.8%)	*< 0.001*

The statistical significance is defined as $p < 0.05$

ESH erythrocyte sedimentation rate, *CRP* C-reactive protein, *GIS* gastrointestinal

The rates of arthritis, abdominal pain, scrotal involvement, relapses, and level of acute-phase reactants were also significantly more frequent in patients with homozygous exon 10 mutations. In addition, arthritis, scrotal involvement, and relapses were common in compound exon 2 and 10 heterozygous mutations. Table 3 depicts the patient characteristics according to *MEFV* mutation types. When patients with exon 2 or 3 variants were compared to the ones without any mutation, no statistically significant difference regarding organ involvement or acute-phase reactant levels were found (arthritis, $p = 0.295$; abdominal pain, $p = 0.250$; scrotal involvement, $p = 0.647$; renal involvement, $p = 0.145$; ESR, $p = 0.781$; and CRP, $p = 0.147$).

One hundred and two patients (42.8%) developed symptoms of FMF during the follow-up period and were put on colchicine therapy based on clinical findings and *MEFV* mutation analysis. Among these patients, all the patients with homozygote p.M694V, p.M680I, pV726A, and pM694I mutations and heterozygote p.M694V/p.M680I and p.M694V/pV726A mutations were started the colchicine treatment. Also, 37 patients with heterozygote p.M694V mutation, 11 patients with heterozygote p.M680I, 6 patients with heterozygote pV726A, and 4 with heterozygote pM694I mutation were started the colchicine treatment in case of an FMF attack during the follow-up, elevated acute-phase reactants, and existence of family history.

Direct immunofluorescence study of biopsy specimens of HSP patients

Renal biopsy was performed in 75, and skin biopsy was performed in 63 of the patients. Leukocytoclastic vasculitis was detected in all of the skin biopsies. Fifteen kidney and 39 skin biopsies were performed in the group with positive *MEFV* gene mutation. IgA depositions were detected in 21 (38.9%) of them. A total of 84 (60 kidney, 24 skin) biopsies were performed in the non-mutation group, and 79 (94%) biopsy specimens had IgA deposition (Fig. 1). Immunofluorescence studies of biopsy materials in mutation (+) and (−) patients revealed that IgA deposits were significantly more common in mutation (−) group whereas IgG and C3 deposits were more frequent in mutation (+) group. Among 33 *MEFV* gene mutation (+) patients who had no IgA deposition on biopsy, there were 18 patients with exon 10 homozygote, 11 patients with exon 10 heterozygote, 2 patients with exon 10 compound heterozygote, 1 patient with exon 2 homozygote, and 1 patient with exon 2 heterozygote mutations.

Table 3 Clinical features and laboratory features of patients when grouped according to *MEFV* mutation type

	Exon 10 homozygous ($n = 31$)	Exon 10 heterozygous ($n = 134$)	Exon 2 and 10 compound heterozygous ($n = 22$)	Exon 2 or 3 homo-heterozygous ($n = 51$)	p
Age, years	8.2 ± 3.7	8.1 ± 3.3	8.2 ± 4.2	8.2 ± 3.4	0.478
Sex, *n* (%), male	20 (64.5%)	78 (58.2%)	12 (54.5%)	31 (60.7%)	0.841
Arthritis	22 (71.0%)	72 (53.7%)	15 (68.1%)	20 (39.2%)	*< 0.001*
Abdominal pain	27 (87.1%)	91 (67.9%)	14 (63.6%)	23 (45.0%)	*< 0.001*
Scrotal involvement	8 (25.8%)	11(8.2%)	5 (22.7%)	3 (5.8%)	*0.010*
Renal involvement	13 (41.9%)	53 (39.6%)	5 (22.7%)	16 (31.3%)	0.055
Elevated ESH	30 (96.8%)	118 (87.3%)	19 (86.4%)	34 (66.6%)	*0.002*
Elevated CRP	30 (96.8%)	110 (82.1%)	16 (72.7%)	31 (60.7%)	*0.019*
Relapse	7 (21.2%)	9 (6.7%)	3 (13.6%)	2 (3.9%)	*0.029*

The statistical significance is defined as $p < 0.05$

ESH erythrocyte sedimentation rate, *CRP* C-reactive protein

Discussion

In this retrospective study, we sought to investigate *MEFV* mutations and their clinical and laboratory finding associations in HSP patients. This cohort represents one of the largest series of patients with association of HSP and FMF. The patients in our center are mainly coming from Central Anatolia, where the FMF disease is most common in our country. The association of HSP with FMF, with a frequency of 10% was first reported by Flatau et al. in 1982 [11]. Since then, several reports addressing the connection between HSP and FMF have been increasingly published [6, 12–16]. Among the studies performed on HSP patients, Ozcakar et al. showed *MEFV* gene mutations in 34% of their HSP patients, which was higher than healthy individuals, while Bayram et al. reported a mutation rate of 44%, which was twofold higher compared to the carrier rate of Turkish population. The results of our study revealed the frequency of *MEFV* mutations as 21.2% [12, 14].

The rate of *MEFV* mutation carrier status in healthy Turkish individuals was reported as 20%, and more than half of these patients had p.E148Q variants [17]. p.M694V is known to be present in only 3% of the general population in Turkey and is known to be the most common mutation in patients with FMF and is rarely detected in the healthy controls [17]. In our study, the frequency of *MEFV* mutations was similar to healthy Turkish population but p.M694V mutation was the most frequent one among all mutation types with a frequency of 52.9%. Only 44 out of 238 of our patients had p.E148Q variants. Studies reported that people carrying p.E148Q variant had no clinical features of FMF; thus, disease-causing role of this mutation is controversial [18]. Accordingly, we did not find any difference between patients with p.E148Q variants and those without a *MEFV* gene mutation.

Although controversies exist about the issue that *MEFV* gene variants predispose to HSP, many studies suggested that *MEFV* gene mutations are related with early disease onset, presence of edema, gastrointestinal, joint and urogenital system involvement, and higher acute-phase reactant levels [4, 5, 12, 14]. Gershoni-Baruch et al. reported that 27% of 52 HSP patients had at least one *MEFV* mutation, but they did not find any difference in clinical, laboratory, and demographic features

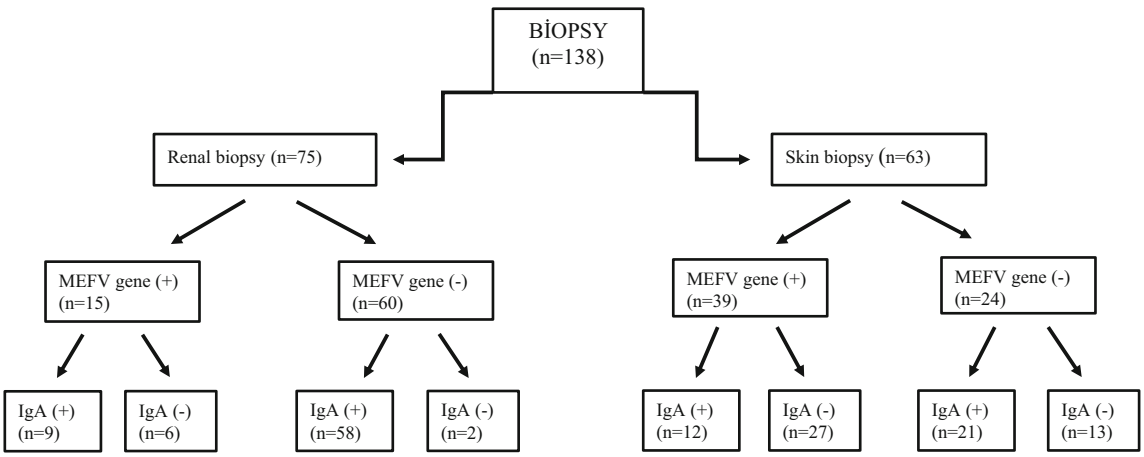

Fig. 1 Direct immunofluorescence study of biopsy specimens

among patients with and without mutations [6]. One recent study from Egypt showed that *MEFV* mutations in HSP patients did not result a differentiation in clinical characteristics, outcome, and laboratory parameters [19]. In our study, *MEFV* mutations affected the HSP course in terms of arthritis, abdominal pain, scrotal involvement, relapse, and higher acute-phase reactant levels. Renal involvement even in terms of proven nephritis with biopsy and long-term outcome did not differ between mutation-positive and mutation-negative patients.

We also formed groups according to mutation subtypes. Among four subgroups, mutations located in exon 10 (including p.M694V mutations) significantly affected the clinical course of HSP. Serum levels of acute-phase reactants were also significantly higher among this subgroup of patients. In patients with exon 10 mutations, abdominal pain, arthritis, scrotal involvement, relapse rate, and acute-phase reactant levels were significantly higher in the homozygous group compared to the heterozygous ones which we believe reflected the upregulated inflammation state in those patients.

The pathological description of HSP is leukocytoclastic vasculitis. In the skin, deposition of IgA (principally IgA1) in dermal capillaries and postcapillary venules is characteristic. In the kidneys, the principal lesion is endocapillary proliferative glomerulonephritis with an increase in endothelial and mesangial cells. Proliferative glomerulonephritis ranges from focal and segmental lesions to severe crescentic disease. There may be marked interstitial inflammatory disease but vasculitis per se is usually not present. Fluorescence microscopy confirms deposits of Ig principally IgA often accompanied by IgG, fibrin, C3, and properdin [20]. These deposits are invariably in mesangial cells, but peripheral capillary loops may be involved in more severe cases. The finding of vascular IgA-dominant immune deposition on DIF examination of the involved skin, gut, and glomeruli has been strongly associated with HSP. Some groups, including the Chapel Hill Consensus Group, incorporated IgA deposition into the definition of HSP [21–23]. Many authors claimed that patients with HSP who had FMF as well had a more severe course but did not provide any details about the pathological examinations in these patients [5, 16]. Majeed et al. found that among 80 patients with HSP only 6 had *MEFV* mutations and the skin biopsy of 1 patient showed leukocytoclastic vasculitis, DIF study showed deposits of IgG and C3 within capillary walls through the upper dermis, and IgA deposition was not seen [24]. In another study, skin biopsies were performed in 9 of 12 patients with FMF and HSP and all showed leukocytoclastic vasculitis but comment on Ig A deposition was not made [4]. Nickavar and Ehsanipour published a case of an FMF patient with HSP whose renal biopsy was reported as crescentic glomerulonephritis without IgA deposits [25]. In our study, 54 biopsies were performed in 238 patients with positive *MEFV* gene mutations. Of these biopsy specimens, 33 did not show IgA deposition and most of these patients had exon 10 mutations. Furthermore, in some of our patients, IgG, IgM, and C3 deposition without IgA was noted. A recent review pointed out that HSP associated with *MEFV* mutations differed from typical isolated HSP. The review summarized several studies in most of which biopsies showed no deposits of IgA and patients experienced recurrence of HSP and atypical rashes. Authors suggested that vasculitis detected in these patients should be considered as an atypical manifestation of FMF rather than a separate disease [9]. Our study supported these findings in terms of the absence of IgA deposits in the majority of patients with *MEFV* mutations and relapses being more common in patients with *MEFV* mutations. Arthritis and abdominal pain, which are the main clinical findings of FMF patients, were significantly more common as well in HSP patients with *MEFV* mutations. These findings rise the doubt and controversion about whether this clinical manifestations may be considered to be associated with FMF as part of what we call FMF rather than as co-existing additional separate clinical entities.

FMF is an autosomal recessive disorder characterized by recurrent attacks of fever and polyserositis including peritonitis, pleuritis, and arthritis. Skin involvement is less common. Erysipelas-like erythema, which usually affects the lower extremity, is the most common cutaneous manifestation; however, nonspecific purpura may also be seen. In a study by Majeed et al., purpura was the most frequent cutaneous manifestation of FMF [24]. Twelve out of 46 FMF patients (26%) had 31 episodes of non-specific purpuric rash. In the same study, the frequency of cutaneous manifestations decreased with colchicine treatment. We believe some of the rashes we defined as HSP might have been a clinical feature of FMF itself.

FMF is prevalent among eastern Mediterranean populations, mainly in non-Ashkenazi Jews, Armenians, Turks, and Arabs, in as many as 1/500 persons. The carrier frequency in non-Ashkenazi Jews is 1:5, Arabs 1:16, Turks 1:5, and Armenians 1:7 [17]. Following the identification of the MEFV gene, FMF has been increasingly reported from all around the globe; however, a large proportion of all FMF patients in the world live in Turkey. Because of the high prevalence of FMF and related amyloidosis in our country and social-economic limitations in admission of patients to a tertiary center, we studied the *MEFV* gene analysis in all HSP patients to avoid skipping the diagnosis of FMF. The main limitation of this study is its retrospective design and limited molecular techniques that had been used only to investigate 12 well-known variants instead of identifying all the variants by sequencing.

In conclusion, *MEFV* gene mutations in exon 10 were detected more frequently among HSP patients than the general population. Exon 2 variants had no clinical significance, while the presence of exon 10 mutations seemed to affect the clinical presentation and laboratory findings. The lack of IgA deposits in biopsies of majority of the patients with *MEFV* gene mutations put doubt on the co-occurrence of HSP and FMF. A plausible explanation would be that the vasculitic rash was an

additional, though rare, manifestation of FMF. Thus, it must be kept in mind that HSP-like rash may be the first presentation of FMF in regions where FMF is common. We believe our FMF diagnosis rate during the course supported this hypothesis and more studies are required to clarify the association.

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Compliance with ethical standards

Disclosures None.

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