

MEFV gene mutations and clinical course in pediatric patients with Henoch-Schönlein purpura

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ABSTRACT

Objective. To determine the frequency of the MEFV gene mutations in pediatric patients diagnosed with HSP and to assess the effect of the MEFV gene mutations on their prognosis.

Material and Methods. Cross-sectional study; pediatric patients between 2-11 years diagnosed with HSP were included. These cases were investigated for 6 MEFV gene mutations (M694V, M680I, A744S, R202Q, K695R, E148Q).

Results. Eighty cases were included in the study of which 55% were male (n= 44). The mean age was 6.44 ± 2.52 years. Disease recurrence occurred in 9 patients, invagination in 5 patients and convulsion in 1 patient during follow-up. Approximately half of the patients received steroids. The MEFV gene mutations was not detected in 44 (55%) of the patients. There was a heterozygous mutation in 19 (22%). E148Q was found in 8 patients, M694V in 5 patients, A744S in 4 patients, and the R202Q heterozygous mutation in 2 patients. The M680I homozygous mutation was detected in 1 patient and the M694V homozygous mutation in 1 patient. The compound heterozygous MEFV gene mutations was found in 15 patients. The presence of the MEFV gene mutations was not correlated with the frequency of renal and gastrointestinal involvement and prognosis, the development of complications and the use of steroids.

Conclusion. The presence of the MEFV gene mutations does not correlate with the clinical course and complication in Turkish pediatric patients with HSP.

Keywords: Henoch-Schönlein purpura, familial Mediterranean fever, MEFV gene.

<http://dx.doi.org/10.5546/aap.2018.eng.e385>

To cite: Can E, Kılınç Yaprak z, Hamilçikan S, et al. MEFV gene mutations and clinical course in pediatric patients with Henoch-Schönlein purpura. *Arch Argent Pediatr* 2018;116(3):e385-e391.

INTRODUCTION

Henoch-Schönlein purpura (HSP) is the most prevalent leukocytoclastic vasculitis in childhood, characterized by non-thrombocytopenic palpable purpura, abdominal pain, arthritis or arthralgia, and nephritis.¹⁻³ Many factors have been identified in its etiology.^{1,2} Familial Mediterranean fever (FMF) has an autosomal recessive transition, progresses in attacks, and involves peritoneum, synovium, pleura, and (rarely) pericardium, together with a high fever most of the time.⁴ The coexistence of FMF and HSP has been shown in studies.^{1,3,5} The frequency of HSP and the MEFV gene mutations has been reported to be 10%.⁶ Some studies have shown that the prevalence of FMF among patients with HSP is increased compared to the general population.^{7,8} The MEFV gene mutations may affect the course of HSP and laboratory findings. Also, MEFV gene mutations are known to exaggerate inflammatory response in HSP.^{8,9} However, there is no full consensus on the effect of the presence of the MEFV gene mutations on joints, gastrointestinal involvement, and long-term prognostic indicators. With patients in whom the MEFV gene mutations has been detected being different clinically and in terms of course and attack frequency, it has been claimed that HSP findings might be a rare form of FMF emergence.⁹ The four most commonly reported mutations in MEFV gene were M694V, M680I, V726A and E148Q.¹⁰ For this coexistence, some studies have posited that the frequency of the MEFV gene mutations especially the V726A mutations, increases in HSP patients, although no differences have

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Funding:
None.

Conflict of interest:
None.

Received: 8-2-2017
Accepted: 10-23-2017

been found in clinical and laboratory findings.¹¹ In other study the most common *MEFV* gene mutations reported were p.M694V (41.15%), p.E148Q (20.35%), p.M680I(G/C) (12.39%) and p.R761H (9.73%) in Turkish population.¹²

The *MEFV* gene mutations encodes the pyrine protein, that plays an important role in inflammatory pathways by decreasing inflammation, significantly in neutrophils; so, the mutated protein may then cause uncontrolled inflammation and predisposing development of HSP and other varieties of vasculitis.¹² Vasculitides may be a clinical feature of FMF with a higher familiar prevalence. *MEFV* gene mutations may act as a genetic susceptibility factor for vasculitides in FMF patients.¹³ Mutation carriers may show higher inflammatory responses with severe clinical symptoms; furthermore, analysis has indicated that the abnormal clearance of immune complexes and dysregulation of inflammatory response were due to defective genetic loci.¹²

We aimed to study determine the frequency of the *MEFV* gene mutations in patients aged 2-11 years diagnosed with HSP and to assess the effect of the presence of the *MEFV* gene mutations on their prognosis.

MATERIAL AND METHODS

Study design

In this cross-sectional study, was carried out a research center outpatient clinic in Istanbul between May 2012 and May 2015 and whose *MEFV* gene mutation analysis was carried out were included in the study. All of the cases in a pediatric age group (2-11 years) diagnosed with HSP were included to study. Patients without informed consent, > 18 years of age, patients with additional chronic disease other than HSP, patients with no *MEFV* gene analysis or no results were excluded to the study. The frequency of HSP and the *MEFV* gene mutations has been reported to be 10%.¹⁰ Based on previous findings, we assumed that the sample size of this study 80 ($\alpha=0.05$, power= 80%). The α level was set at 0.05, based on a two-sided, two-sample *t*-test.

Demographic and clinical parameters such as age, gender, application complaints, application seasons, precence of the susceptible etiological factors (upper-respiratory tract infection, insect bite history, hepatitis B serology, serum antistreptolysin O (ASO) level), precence of corticosteroid therapy and *MEFV* gene mutations analysis results of these cases were recorded

during the outpatient-clinic examination. The duration of hospitalization, fecal occult blood and gastrointestinal involvement, proteinuria and hematuria, and renal involvement presence were recorded in HSP patients with FMF coexistence. The gender, age, diagnosis dates, history of infection before the disease, vaccination, insect bites, and application complaints of the patients were recorded. The clinical findings on skin, joints, kidneys, the gastrointestinal system, and other systemic involvements were examined in detail, both at the beginning of and during the disease. HSP was diagnosed according to the established criteria of the final EULAR/PRINTO/PRES HSP criteria. (Table 1).¹¹ Complications was considered as the development of hypertension, invagination, and convulsion. The hepatitis serology was assessed with blood serum HbsAg and anti Hbs seropositivity. In ASO levels, the levels above 200U/ml were regarded as positive. Skin biopsy; can not done in selective patient for HSP because of the clinical inability.

Duration of patients follow up period was continued along study period. All patients were evaluated with clinical and laboratory assessment for renal and gastrointestinal involvement or persisting arthritis or arthralgias. Approval was taken from Hospital ethics committee and informed written consent was taken from the patients in accordance with the Declaration of Helsinki.

Laboratory analysis of *MEFV* gene mutations

All children were screened for six *MEFV* gene mutations (M694V, M680I, M694I, V726A, K695R, E148Q) using the FMF Strip Assay, Vienna Lab Diagnostics GmbH, Vienna, Austria. Genomic DNA was extracted from 5 ml of peripheral blood with ethylenediamine tetraacetic acid (EDTA) by standard procedures. The assay is based on the Light Cycler real-time quantitative polymerase chain reaction (RT-PCR) and reverse hybridization, suitable for the determination of the *MEFV* mRNA expression. It includes PCR amplification with a thermo cycling program of 35 cycles (94 °C for 15 seconds, 58 °C for 30 seconds, and 72 °C for 30 seconds) with the final extension at 72 °C for 3 minutes, followed by the hybridization of the amplification products to a test strip containing both wild and mutant allele-specific oligonucleotide probes immobilized as an array of parallel lines. Bound biotinylated sequences were detected using streptavidin-alkaline phosphatase and enzymatic color

reactions. For each polymorphic position, one of three possible staining patterns was obtained: a wild-type probe only (normal genotype), a wild-type and mutant probe (heterozygous genotype), or a mutant probe only (homozygous mutant genotype).

Statistical analysis

Statistical analyses were carried out using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). In addition to the descriptive statistical methods (mean, standard deviation) in the assessment of the data, an independent *t*-test was used in the comparison of binary groups, the chi-square and Fisher Exact Test was used in the qualitative data comparisons. The results were assessed at the significance level of $p < 0.05$.

RESULTS

Total 80 patients included to study. Of the cases, 44 (55%) were male and 36 (45%) were female, and the mean age was 6.44 ± 2.52 years.

The most frequent application complaints in the cases were skin rash in 67 patients (83.75%), joint pain in 7 patients (8.75%), abdominal pain in 5 (6.25%), and convulsion in 1 patient (1.25%). Fecal occult blood was found in 48 (60%) cases, hematuria in 20 (25%) cases, proteinuria in 18 (22.5%), and joint involvement in 46 (57.5%) of the cases. The season with the highest number of applications was winter (41%). Among etiological factors, 38 (47.5%) patients had a history of the upper-respiratory tract infection, 1 (1.2%) patient had a history of a bee sting, and 2 (2.5%) patients were found to be hepatitis B positive.

The *MEFV* gene mutations was found in 36 (45%) of the cases with HSP, with 19 (23.7%) patients having the heterozygous mutations. The mean age of the cases, of which the *MEFV* gene mutations was heterozygous, compound heterozygous, and homozygous positive, was 7.22 ± 2.57 years. The mean age of the patients in whom the *MEFV* gene mutations was not found was 5.80 ± 2.31 years. Comparing age distribution, the mean age of the pathological FMF group was

TABLE 1. Final EULAR/PRINTO/PRES Henoch-Schönlein purpura criteria and classification definition

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
Purpura (mandatory criterion)	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, *not related to thrombocytopenia.	89	86	87.5
1. Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding.	61	64	62.2
2. Histopathology	Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit.	93	89	91.1
3. Arthritis or arthralgias	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion.	78	42	59.9
4. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample. Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or $\geq 2+$ on dipstick.	33	70	51.4
HSP EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.96)	Purpura or petechiae (mandatory) with lower limb predominance* and at least one of the four following criteria: Abdominal pain Histopathology Arthritis or arthralgia Renal involvement.	100	87	93.5

*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.

AUC, area under the curve; EULAR, European League Against Rheumatism; HSP, Henoch-Schönlein purpura; PRES, Paediatric Rheumatology European Society, PRINTO, Paediatric Rheumatology International Trials Organisation

found to be statistically significant ($p=0.01$). No statistically significant difference was observed between gender distribution in the *MEFV* gene mutations groups (Table 2).

E148Q was found in 8 (10%) patients, M694V in 5 (6.25%) patients, A744S in 4 (5%), and the R202Q heterozygous mutations was found in 2 (2.5%) patients. The M608I homozygous mutations was detected in 1 (1.25%) patient and the M694V homozygous mutations in 1 (1.25%) patient. The compound heterozygous *MEFV* gene mutations was identified in 15 (18.7%) patients (Table 3).

During the follow-up, invagination was found in 1 (1.25%) patients, hypertension development in 2 (2.5%) patients, and convulsion in 1 (1.25%) and recurrence was found in 5 (6.25%) patients.

Corticosteroid therapy was 17 (47.2%) in the *MEFV* gene mutation group and 20 (45.45%) in the *MEFV* negative group. Complication rate was 4 (11.1%) in the *MEFV* mutation group and 5 (11.36%) in the *MEFV* negative group. There was not observed between the presence of the *MEFV* gene mutations and disease severity requiring the use of steroids ($p=0.875$) and no significant difference was observed between complication development and the presence of the *MEFV* gene mutations ($p=0.972$).

DISCUSSION

HSP is generally reported to show up between the ages of 5 and 15 years, around ages 5-6 years on average.^{1,2,16,17} The cases in our study group were between 2 and 11 years, with an age average of 6.44 ± 2.52 years. The age average in the patients in whom *MEFV* gene mutations was detected was 7.22 ± 2.57 years, which was higher

when compared to the group in which mutations was not found. The reason for the delay in the mean age is explained by the fact that the mean age of newly diagnosed patients is high. Genetic analysis was performed when patients were clinically considered HSP. The male/female ratio in the disease has been reported as being 1.5:1 and 1.8:1.^{1,16,17} However, the present study revealed a ratio of 1.2:1. There was no difference between the groups with and without *MEFV* gene mutations, nor in gender distribution within those groups.

It is known that the frequency of FMF increases in patients with HSP.^{7,8} Different mutational prevalences have been reported in studies done in different centers in Turkey in relation to *MEFV* mutations in children with HSP. In a study carried out by Özcakar et al., on 80 patients,

TABLE 3. Mutations and complication profiles of Henoch-Schönlein purpura cases with Familial mediterranean fever

Detected mutations	FMF (+) n: 36	%
Heterozygote mutations	19	23.7
E148Q	8	10
M694V	5	6.25
A744S	4	5
R202Q	2	2.5
M608I homozygotes	1	1.25
M694V homozygotes	1	1.25
Compound heterozygotes	15	18.7
Follow-up		
No complications	71	88.75
Invagination	1	1.25
Hypertension	2	2.50
Convulsion	1	1.25
Recurrence	5	6.25

TABLE 2. Demographic and clinical comparison of Henoch-Schönlein purpura cases with Familial mediterranean fever

	FMF (-) n:44		FMF (+) n:36		<i>p</i>
Age (years)	5.80 ± 2.31		7.22 ± 2.57		0.01
Gender					
Male	25	56.82%	19	52.78%	0.71
Female	19	43.18%	17	47.22%	
Application complaints					
Non-palpable purpura	44	100%	36	100%	NS*
Occult blood screen	25	56.8%	23	63.8%	NS
Hematuria	11	25%	9	25%	NS
Proteinuria	8	18.1%	10	27.7%	NS
Joint involvement	22	50%	24	66.6%	NS
Stool occult blood	22	%50	26	72.2	NS

*NS: not significant($p > 0.05$)

the frequency of the *MEFV* gene mutations was reported to be 34%. Only the heterozygous mutations was observed in these patients and no homozygous or compound heterozygous patients were identified.⁴ Bayram et al.,⁸ the heterozygous mutations was seen in 31% of 107 patients and homozygous/compound heterozygous mutations were found in 13%. Altug et al., shown that 18 (26%) had *MEFV* mutation of 68 HSP patients. Cases mutation analysis obtained 15 (22%) patients were heterozygous for one of the screened *MEFV* mutations, while three (4.5%) patients were compound heterozygous for two of the studied mutations, and one (1.5%) patient was homozygous for E148Q/E148Q.¹³ Dogan et al. reported that 11 of 76 patients (14.4%) were heterozygous (E148Q in 5, M694V in 4, M680I in 1, E148V in 1), 5 (6.6%) were homozygous (M694V/M694V in 4, V726A/V726A in 1), and 2 (2.6%) were compound heterozygous (E148Q/M694V mutations in 1 and L110P/E148Q mutations in 1).¹⁴ With a frequency of *MEFV* gene mutations in our study of 45%, mutations were detected in 19 (23.7%) of the HSP patients who were heterozygous, whereas 15 (18.7%) had compound heterozygous *MEFV* gene mutations, and the homozygous mutations was found in 2 (2.5%) patients. This differs from the results of the study done by Bayram et al.,⁸ in which 70% of HSP patients with *MEFV* gene mutations had heterozygous mutations, 12.7% had compound heterozygous mutations, and 17% had homozygous mutations. E148Q was the foremost common mutations detected in our HSP study group, which does not line up with the results of other Turkish studies, which found that M694V was the most common mutations.^{4,8} Our results are, however, in line with the results of the studies by Gershoni et al.,⁷ from Israel and He et al.,²⁰ from China, in which E148Q was the foremost frequent mutations among patients with HSP (43% and 85%, respectively).

It has been reported that HSP is more prevalent in autumn, spring, and winter months.^{1,2,18} Considering that upper-respiratory tract infections, which are believed to play a role in the etiology of the disease, increase in these seasons, the prominence of colder months has been found to be significant. The infectious factors reported in the literature are Group A Beta Hemolytic *Streptococcus* (GABHS), *Mycoplasma pneumoniae*, *Toxocara canis*, *Yersinia*, *Legionella*, *Helicobacter pylori*, *Campylobacter jejuni* enteritis, *Bartonella henselae*, Varicella Zoster virus, Rubella

virus, hepatitis B and A viruses, EBV, HSV, CMV, HIV, and HPV.²¹⁻²⁶ In our study, hepatitis B positivity was found only in 2 cases with viral factors. Triggering factors such as vaccination and insect bites are mentioned in the literature;^{27,28} one patient had the history of a bee sting in our study.

HSP is generally diagnostic since it has palpable purpura characteristics observed more intensely in the lower extremities and can range from small petals to wide ecchymoses. In our study, it was found that non thrombocytopenic palpable purpura was the only finding seen in all the cases, just as in various publications in the literature. Joint involvement is reported to be the second most widespread finding.^{2,18,19} In our study, gastrointestinal involvement and joint involvement were observed at a frequency of 60% and 57.5%, respectively, a similar frequency as those in the literature.^{2,18,29}

While abdominal pain and fecal occult blood positivity have been observed in gastrointestinal involvement, invagination has been reported to be the most frequent complication. In our study, invagination developed in five cases, which were improved by a laparotomy. The incidences of laparotomies performed when surgical complications develop are 5-22.4%, as reported in previous studies.^{30,31} In our study, no statistically significant difference was observed between joint involvement and gastrointestinal involvement and the presence of the *MEFV* gene mutations.

Renal involvement rates have been reported to be 15-62% in HSP,^{2,14,18,29} with renal involvement mostly occurring in the first four weeks of the disease and the possibility increasing in those with persistent purpura and/or severe gastrointestinal involvement.³² However, in some studies carried out, of renal failure frequency connected to HSP is reported to be 0-3%.^{14,29} Similarly, no statistically significant difference was observed between renal involvement and the presence of *MEFV* gene mutations in the studies of Altug et al. and Dogan et al.^{13,14} While hematuria was observed in 25% of our patients, the proteinuria ratio was 22.5%. In proteinuria at the nephrotic level, or at later stages, renal failure was not observed in any of our patients; no renal biopsies were carried out for any patient. No statistically significant difference was observed between the *MEFV* gene mutations presence and renal involvement.

In HSP patients generally recover with support treatment. However, corticosteroid

treatment may ensure a decrease in symptoms in patients with severe gastrointestinal involvement and arthritis. Corticosteroid treatment does not affect the prognosis of renal involvement, does not reduce the duration of the disease, and does not prevent relapses.³³ In this study, 53.75% of our patients benefited from resting in bed, from hydration, and from non-steroid anti-inflammatory medicines. Steroid treatment was added to the remaining 46.25% of the patient group. There was no statistically significant difference between the use of steroids and the presence of the *MEFV* gene mutations.

In summary, in the present study, no relationship was found between the presence of the *MEFV* gene mutations and the clinical course of the disease and between complication development in pediatric patients with HSP and treatment requirements. ■

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