MEFV Mutations Modify the Clinical Presentation of Henoch-Schönlein Purpura

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ABSTRACT. ***Objective.*** To investigate the prevalence of *MEFV* gene mutations in Turkish patients with Henoch-Schönlein purpura (HSP) but with no symptoms of familial Mediterranean fever (FMF). In addition, we assessed the clinical and laboratory characteristics of HSP patients with and without *MEFV* mutations.

Methods. Eighty pediatric patients with HSP (44 boys and 36 girls) were enrolled. Blood for mutation analysis was obtained either at the time of the diagnosis of HSP or during followup visits in previously diagnosed patients. No patient had the diagnosis of FMF in their history and in the followup period. Exon 10 of the *MEFV* gene was screened, together with p.E148Q mutation analysis.

Results. Twenty-seven (34%) patients were found to be heterozygous for one of the screened *MEFV* mutations; p.M694V in 16, p.M680I in 5, p.V726A in 3, and p.E148Q in 3 patients. Patients with *MEFV* mutations were younger than those without mutations and they had edema and arthritis more frequently. Also, the frequencies of elevated erythrocyte sedimentation rate and C-reactive protein values were found to be significantly higher in patients who had *MEFV* mutations.

Conclusion. Alterations in the *MEFV* gene are important susceptibility factors for the development of HSP and also affect the clinical presentation of it. (First Release Oct 1 2008; J Rheumatol 2008;35:2427–9; doi:10.3899/jrheum.080405)

Key Indexing Terms:
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Henoch-Schönlein purpura (HSP) is among the most common vasculitides of childhood. It is an IgA immune complex-mediated small-vessel vasculitis that classically presents with the triad of nonthrombocytopenic palpable purpura, colicky abdominal pain, and arthritis. The exact causative factor is not known; however, both genetic and environmental factors are thought to play a role in the development of vasculitis like HSP[1]. Increased frequency of both HSP and polyarteritis nodosa (PAN) have been reported in patients with familial Mediterranean fever (FMF)[2,3]. Thirty-eight percent of patients with PAN[4] and 30% of patients with various childhood rheumatic diseases[5] were found to carry *MEFV* gene mutations. Similarly, patients with HSP in Israel have been investigated for the presence of *MEFV* mutations and 27% of the patients were found to have *MEFV* mutations[6]. The purpose of our study was 2-fold; first, to investigate the prevalence of *MEFV* gene mutations in Turkish patients with HSP who had no symptoms of FMF; and second, to assess the clinical and laboratory characteristics of HSP patients with and without *MEFV* mutations.

MATERIALS AND METHODS

Eighty pediatric patients who had been followed in 4 centers in Turkey between September 2006 and January 2008 were enrolled. All patients fulfilled the European League Against Rheumatism/Pediatric Rheumatology European Society endorsed consensus criteria for the diagnosis of HSP[7]. Patients with established or suspected diagnosis of FMF according to the Livneh criteria[8] were excluded, including 6 patients with homozygous mutations that were diagnosed after HSP. These 6 patients were admitted to the hospital with the clinical findings of HSP; 5 of them had FMF symptoms before the onset of HSP and one developed FMF symptoms during the followup period after HSP diagnosis. All had elevated acute-phase reactants during HSP attack and colchicine was started in all patients. A questionnaire that included the clinical characteristics and laboratory features of the patients was completed by the physicians. Blood for mutation analysis was obtained either at the time of diagnosis of HSP or during followup visits in previously diagnosed patients. Written informed consent was obtained

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from the parents of each patient and the study was approved by the Institutional Ethics Committee.

DNA was isolated from peripheral blood lymphocytes by standard procedures. Exon 10 of the *MEFV* gene was screened using direct sequencing of the polymerase chain reaction (PCR) amplified fragments. Cycle sequencing kits (Beckman Coulter, Fullerton, CA, USA) and a Beckman Coulter CEQ 2000 XL automated sequencer were used during these investigations. The p.E148Q mutation was analyzed with a reported restriction fragment length polymorphism-PCR protocol[9,10].

The results were analyzed by using SPSS for Windows 11.5 and descriptive statistics are presented as percentages, medians, means, and standard deviations. Comparisons between the 2 groups were evaluated by Student t test, Mann-Whitney U-tests, or chi-squared test where applicable. A p value < 0.05 was considered statistically significant.

RESULTS

The study group consisted of 80 patients (44 boys and 36 girls) with HSP. Mean age at the time of the diagnosis of HSP was 7.8 ± 2.8 (range 2 to 13.5) years. Twenty-seven (34%) patients were found to be heterozygous for 1 of the screened *MEFV* mutations: p.M694V in 16, p.M680I in 5, p.V726A in 3, and p.E148Q in 3 patients. Clinical and laboratory characteristics of the patients with and without *MEFV* mutations are summarized in Table 1. Patients with *MEFV* mutations were younger than those without mutations, and they had edema and arthritis more frequently. Elevated erythrocyte sedimentation rate (ESR) was found to be significantly higher in patients who had *MEFV* mutations. The frequency of elevated C-reactive protein (CRP) values was not different between the 2 groups when 0.5 mg/dl was used as a cutoff value (p = 0.11). However, when the cutoff value of 10 times normal was used, the frequency of elevated CRP values was found to be significantly higher in patients with *MEFV* mutations.

DISCUSSION

Table 1. Clinical and laboratory findings of patients with Henoch-Schönlein purpura.

	Patients without *MEFV* Mutations, n = 53 (%)	Patients with *MEFV* Mutations, n = 27 (%)	p
Mean age at the diagnosis, yrs	8.3 ± 3.0	6.9 ± 2.3	**0.03**
Sex, n (%)			
Female	23 (43)	13 (48)	0.68
Male	30 (57)	14 (52)	
Clinical findings			
Purpura	53 (100)	27 (100)	
Edema	18 (34)	16 (60)	**0.03**
Abdominal pain	35 (66)	18 (67)	0.95
Arthritis	23 (43)	17 (63)	0.09
Renal involvement	19 (36)	11 (41)	0.66
Laboratory features			
Leukocytosis, n = 76	12 (23)	9 (38)	0.19
Elevated ESR, n = 76	27 (52)	22 (92)	**0.001**
Elevated CRP, n = 67	4 (9)	7 (35)	**0.01**

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

Our study showed that *MEFV* mutations were important genetic predisposing factors in HSP. Twenty-seven of 80 (34%) pediatric HSP patients were found to carry 1 of the screened *MEFV* mutations. Moreover, patients with *MEFV* mutations had some significant differences concerning the clinical presentation and laboratory features of HSP; they were younger, they had edema and arthritis more frequently, and they had higher ESR and CRP values than those without *MEFV* mutations.

Previously, the carrier rate of *MEFV* mutations in healthy Turkish individuals has been reported as 20%. However, more than half of those people had p.E148Q mutation[11]. Many people carrying homozygote p.E148Q mutation have no clinical features of FMF; thus, the disease-causing role of this mutation is controversial[12]. In our study, only 3 out of 27 patients had p.E148Q mutation; that is, approximately 90% of our patients had non-p.E148Q mutations. Morover, 60% of our study group had p.M694V mutation, which was detected in only 3% of the general population in Turkey. These are important findings because pM694V mutation is known to be the most common mutation in patients with FMF and is rarely detected in the healthy controls. Indeed, 3 cases of severe vasculitis (2 HSP and 1 protracted febrile myalgia) in 4 siblings with FMF were recently described, and 2 of these 3 siblings had p.M694V homozygosity[13]. Thus, our results suggest that the mutations identified in children with HSP are important predisposing factors for disease development.

In another study from Israel, 52 patients with HSP were investigated for the presence of *MEFV* mutations. Those authors found that 9.6% of the patients had homozygous or compound heterozygous mutations and 17.3% had heterozygous mutations. In our study, 34% of the patients had heterozygous *MEFV* mutations, which shows a 2-fold increase as compared to the aforementioned study. The main difference between the 2 studies were with regard to clinical findings. Gershoni-Baruch, *et al* found no difference between the mean age at disease onset and clinical findings of patients with and without mutations[6]. In our study, patients with *MEFV* mutations were found to be younger than patients without mutations. Edema and — although statistically insignificant — arthritis were more frequently detected in those patients. In general, subcutaneous edema was reported in 21%–52% of patients with HSP and particularly in the very young children[14,15]. However, in our clinical practice, we have recognized that FMF+HSP patients, whatever the age, developed edema more frequently. Considering the results of our study, it is reasonable to say that in countries where FMF is more prevalent, the presence of *MEFV* mutations affect the clinical presentation of HSP. Therefore, patients with HSP who present with edema and arthritis should be followed more carefully regarding FMF or at least *MEFV* gene carriage.

Other important results from our study were that ESR

and CRP levels were found to be more frequently elevated in patients with HSP who had a heterozygous *MEFV* mutation. When we look at the FMF pathogenesis, *MEFV* gene encodes a protein called pyrin. Pyrin plays a crucial role in the inflammatory pathways of the innate immune system and is believed to decrease inflammation, specifically in neutrophils[16,17]. A mutated pyrin results in augmented inflammation that predisposes patients with FMF and carriers of *MEFV* mutation to have a proinflammatory state. Tunca, *et al*[18] found that CRP and serum amyloid A protein values were significantly higher among FMF carriers than the control group, and proved that *MEFV* heterozygotes have an abnormal phenotype. Lachmann, *et al*[19] also showed that both basal and peak acute-phase protein concentrations were found to be greater in *MEFV* heterozygotes. This upregulated inflammation predisposes these patients to chronic inflammatory diseases and vasculitis like HSP. More frequent elevation of ESR and CRP in patients with heterozygous *MEFV* mutations in our study also confirms this upregulated inflammation. Consequently, HSP patients with elevated acute-phase reactants should be followed carefully, again concerning FMF or at least *MEFV* gene carriage.

Alterations in the *MEFV* gene are important susceptibility factors for the development of HSP and also affect the clinical presentation of the disease. Future genetic studies may identify other likely causative inflammatory genes that might have a role in the pathogenesis of these mysterious vasculitides, and perhaps further genotype–phenotype correlations will then be found.

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