Araştırma Makalesi
Research Article

Effect Of MEFV Variants On The Presentation And Clinical Course Of Henoch-Schonlein Purpura In Children?

ÇOCUKLARDA HENOCH-SCHONLEIN PURPURASININ PREZENTASYONU VE KLİNİK SEYRİ ÜZERİNE MEFV VARYANTLARININ ETKİSİ

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ABSTRACT

Objective: The purpose of this study was to appreciate MEFV variants frequency and the effects of MEFV variants on the clinical course including renal involvement in children with Henoch-Schonlein Purpura (HSP).

Materials and Methods: Children with a diagnosis of HSP who were evaluated for the presence of MEFV variants were enrolled in this study. Patients were separated into two groups according to the presence of MEFV variants. Group 1 included cases without a mutation and Group 2 included cases with a mutation in at least one allele (homozygous, heterozygous or compound heterozygous). We also investigated specifically the effects of M694V mutation on the course of HSP by comparing patients with M694V mutation in at least one allele with patients not carrying M694V mutation.

Results: Forty-seven patients (23 female) were enrolled. MEFV mutation rate (53%) was 3.5 times the rate in general population. M694V was the most common mutation (48%). Patients with MEFV mutations, especially those with M694V mutation, had lower incidence of preceding infection, but increased inflammatory markers, scalp edema and relapse rate. Renal involvement and long-term prognosis were not affected with the presence MEFV mutations.

Conclusions: MEFV variants cause susceptibility to develop HSP and are associated with increased inflammation and altered clinical course. However, renal involvement and long-term prognosis were not affected with the presence of MEFV mutations.

Keywords: Henoch-Schonlein, IgA vasculitis, MEFV gene, renal involvement

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ÖZ

Giriş ve Amaç: Henoch-Schonlein Purpura'lı (HSP) çocuklarda MEFV varyantlarının sıklığı ve renal tutulum dahil klinik seyir üzerindeki etkilerinin değerlendirilmesi amaçlandı.

Yöntemler: Bu çalışmaya MEFV varyantlarının varlığı açısından değerlendirilen HSP tanılı çocuklar alındı. Hastalar öncelikle MEFV mutasyonlarının varlığına göre mutasyonu olmayan hastalar Grup 1 ve en az bir allelde mutasyonu olan (heterozigot, homozigot veya bileşik heterozigot) hastaları içerenler Grup 2 olmak üzere iki gruba ayrıldı. Ayrıca en az bir allelde M694V mutasyonu olan hastaları M694V mutasyonu taşımayan hastalarla karşılaştırarak M694V mutasyonunun HSP seyri üzerindeki etkileri spesifik olarak araştırıldı.

Bulgular: Kırk yedi hasta (23 kadın) kaydedildi. MEFV varyant oranı (% 53) genel popülasyondaki oranın 3,5 katıydı. M694V en yaygın mutasyondu (%48). MEFV varyantlı hastalarda, özellikle M694V mutasyonu taşıyanlarda öncesinde enfeksiyon görülme insidansı daha düşüktü, ancak inflamatuar belirteçler yüksek, skalp ödemi ve nüks oranı fazlaydı. MEFV varyantlarının varlığından böbrek tutulumu ve uzun dönem prognoz etkilenmedi.

Sonuç: MEFV varyantları, HSP geliştirme yatkınlığına neden olmaktadır ve artan inflamasyon değişen klinik seyir ile ilişkilidir. Ancak böbrek tutulumu ve uzun dönem prognoz MEFV varyantlarının varlığından etkilenmemiştir.

Anahtar kelimeler: Henoch-Schonlein, IgA vasküliti, MEFV geni, renal tutulum.

Henoch Schonlein Purpura (HSP), an IgA-associated small vessel immune complex vasculitis, is a very common systemic vasculitis of childhood characterized by varying degrees of cutaneous, intestinal, joint and renal involvement (1). The etiology of HSP has not been fully understood and no specific genetic abnormality has been described. Recently, it has been suggested that class II HLA region may be the major susceptibility locus for HSP (2). On the other hand, underlying genetic milieu of the patients, like the presence of MEFV mutations can influence the clinical presentation and course of HSP in children (3).

Familial Mediterranean Fever (FMF) is an auto-inflammatory disease that emerges due to mutations in the MEFV gene, which codes the protein pyrin (4). While FMF is characterized by recurrent febrile attacks, peritonitis, pleurisy, rash, and arthritis, there can be clinical variability (5). Several studies defined a higher prevalence of MEFV gene variants in association with vasculitis and rheumatologic diseases such as polyarteritis nodosa, juvenile idiopathic arthritis, HSP and inflammatory bowel disease (6-9). IgA vasculitis is the most common vasculitis in FMF patients. It has a prevalence of 2.7-7% (10). Increased inflammatory response caused by MEFV gene mutations may predispose to IgA vasculitis or trigger the development of a vasculitis resembling IgA vasculitis (7-9-10).

The presence of MEFV variants has also been considered to affect the clinical presentation of HSP in countries where FMF is prevalent. Several studies evaluated the impact of MEFV variants on the clinical presentation and course of HSP, but the findings were conflicting (11-19). In general, the presence of MEFV variants did not importantly affect most of the clinical and laboratory parameters evaluated. However, patients with MEFV variants were reported to have more frequent gastrointestinal and joint involvement and higher erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, more common joint involvement, higher rate of subcutaneous edema, two-fold higher relapse rate, higher CRP and ESR levels and were younger at the time of diagnosis (11-15). In addition, patients with

mutations in exon 10 had more prevalent genital involvement, lower hemoglobin, higher leukocyte, thrombocyte, and IgA levels, while M694V and E148Q mutations were specifically associated with higher leukocyte/CRP levels and joint involvement, respectively (16-18). On the other hand, some authors reported that clinical manifestations, such as arthritis, hematuria, gastrointestinal bleeding, and fever were evenly distributed amongst patients with or without MEFV variants (13-14-19). Thus, the impact of MEFV variants on the course of HSP seems not uniform and population studied possibly affected the course of disease.

In this study, we aimed to evaluate the MEFV gene variants rate and mutation types in children with HSP along with the effects of MEFV variants on clinical manifestation (including renal), laboratory findings, and the course of disease in a single center in Western Turkey, where the approximate prevalence of FMF is 1:1000 and the carrier ratio is 1:5 (4).

PATIENS AND METHODS

Children with a diagnosis of HSP who were evaluated for the presence of MEFV mutations were enrolled in this study. As MEFV variants are quite often in HSP than in normal population, and mutation carriers may have more serious clinical symptoms with higher inflammatory response, MEFV mutation analysis was performed in patients who had severe abdominal pain, significant acute phase response, or recurrent clinical findings (16). Written parental informed consent form to participate in the study was acquired from all parents. The protocol was approved by the local ethical committee (2018/23-11).

The diagnosis of HSP was made in accordance with the 2008-EULAR-PRINTO-PRES classification (20). Patient files were retrospectively evaluated regarding demographic, clinical, and laboratory findings at diagnosis, MEFV gene analysis results, and the course of the disease. Clinical findings including abdominal pain and/or gastrointestinal bleeding (hematochezia, melena, or occult blood in stool) were considered as gastrointestinal involvement, while hematuria, proteinuria, and/or increased serum creatinine were considered renal involvement. Other system involvements, if present, were also evaluated. Laboratory parameters included complete blood count, CRP, ESR, serum IgA, serum creatinine, estimated glomerular filtration rate (eGFR), fecal occult blood, and 24-hour urine protein excretion. Patients were primarily assigned into two groups based on the presence of MEFV variants Group 1 included patients without variants and Group 2 included patients with variants in at least one allele (homozygous, heterozygous, or compound heterozygous). We also investigated specifically the effects of M694V mutation on the course of HSP by comparing patients with M694V mutation in at least one allele with patients not carrying M694V mutation.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. Quantitative variables were presented as mean ± standard deviation or median (minimum-maximum) values, whereas categorical variables were presented as number of cases and percent. Groups were evaluated for normal distribution using the Kolmogorov-Smirnov test. Mann Whitney U and Chi-square tests were used to compare the groups for mean values and for comparison of ratios across the groups, respectively. P value <0.05 was considered statistically meaningful.

RESULTS

The total number of children with a diagnosis of HSP followed in our clinic was 201. Among these patients, 47 (23.4%) had MEFV mutation analysis. The demographic, clinical, and laboratory features of these 47 patients were shown in Table 1. The presenting complaint was palpable purpura in all patients. Seven out of 20 (35%) patients with renal involvement had undergone renal biopsy.

Table 1. Demographic, clinical and laboratory data of all Henoch Schonlein purpura patients analyzed for the presence of *MEFV* mutation.

Demographic features	
• Number	47
• Male/female	24/23
• Age at disease onset (years)[1]	8.0 ± 3.5
• Follow-up time (months)[2]	27.2 ± 26.2
Clinical findings [N (%)]	
• Purpura	47 (100)
• Arthritis/arthralgia	28 (60)
• Gastrointestinal involvement	29 (62)
• Renal involvement	20 (43)
• Invagination	4 (9)
• Scalp edema	4 (9)
• Preceding infection	14 (30)
• Orchitis	4 (8.5)
• Relapse	18 (38)
Laboratory results	
• Hemoglobin[3] (g/dL)	12.1 ± 1.2
• Leukocytes[4] (/mm^3)	11.050 ± 4.778
• Platelets[5] (/mm^3)	367.489 ± 141.510
• ESR[6] (mm/h)	30.5 ± 23.3 (2-110)
• CRP[7] (mg/L)	34.0 ± 50.3 (0-233)
• IgA[8] (mg/dL)	166.3 ± 92.8
• Proteinuria [N (%)]	10 (21.2)
• Hematuria [N (%)]	19 (40.4)
Treatment [N (%)]	
• NSAI	6 (13)
• Steroid	29 (62)
• Colchicine	16 (34)
• Azatiophrine	2 (4)
• Mycophenolate mofetil	1 (2)
• Cyclophosphamide	1 (2)
• ACE-I	6 (13)
• Omega-3	2 (4)

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, NSAID: Nonsteroid anti-inflammatory drugs ACE-I: Angiotensin-converting enzyme inhibitors IgA: immunoglobulin A
The variables were presented as mean ± standard deviation[1,2,3,4,5,8] or median (minimum-maximum)[6,7] values, whereas categorical variables were presented as number of cases and percent.

MEFV variants were found in 25 (53%) of these 47 HSP patients. This rate was 3.5-fold higher compared to the prevalence of MEFV gene variants in a sample of the Turkish population including 500 persons aged 5 to 65 years (74/500, 14.8%) (21). The most common MEFV variants were M694V (12 patients, 48%), R202Q (8 patients, 32%), and E148Q (5 patients, 20%) (Table 2). M694V mutation was more common compared to general Turkish population albeit the difference was not significant (12/25 vs 20/74, p=0.053) (21).0,6 mg/dL; p=0,001).

Table 2. Distribution of *MEFV* gene mutations in 47 Henoch Schonlein purpura patients.

	N	**%**
No mutation	22	47
Homozygous mutation		
• M694V / M694V	3	6
• R202Q / R202Q	2	5
Compound heterozygous mutation		
• M694V / R202Q	3	6
• M694V / M680I	1	2
• E148Q / P369S	1	2
Heterozygous mutation		
• M694V / -	5	11
• E148Q / -	4	9
• R202Q / -	3	6
• V726A / -	1	2
• A744S / -	1	2
• K695R / -	1	2

Comparison of clinical and laboratory findings showed that patients in Group 2 had higher platelet and lower hemoglobin levels compared to Group 1. In addition, CRP and ESR tended to be higher in Group 2, albeit insignificantly. However, significantly more patients had elevated CRP in Group 2. In addition, relapse rate was higher in patients with MEFV mutations (Table 3).

Table 3. Comparison of clinical and laboratory findings in Henoch Schonlein purpura patients without (Group 1) and with (Group 2) *MEFV* mutations.

	Group 1 Mutation (-)	Group 2 Mutation (+)	P
Female / Male	11/11	12/13	0.562
Age at diagnosis (years)	7.9 ± 4.1	8.0 ± 2.9	0.948
Preceding infection [N (%)]	9 (41)	5 (20)	0.107
Symptoms [N (%)]			
• Arthralgia / arthritis	13 (59)	15 (60)	0.924
• Abdominal pain	14 (64)	15 (60)	0.798
• Invagination	2 (9)	2 (8)	0.894
• Orchitis	1 (5)	3 (12)	0.355
• Scalp edema	0	4 (16)	0.071
Laboratory results			
• Hemoglobin (g/dL)	12.4 ± 1.0	11.8 ± 1.3	**0.048**
• Leukocytes (/mm^3)	10.544 ± 3838	11.642 ± 5702	0.790
• Platelets (/mm^3)	317.720 ± 100.640	424.045 ± 161.212	**0.021**
• ESR[1] (mm/h)	29 ± 19	35 ± 14	0.114
• Elevated ESR[2] [N (%)]	12 (55)	19 (76)	0.121
• CRP[3] (mg/L)	24 ± 36	44 ± 55	0.091
• Elevated CRP[4] [N (%)]	14 (64)	22 (88)	**0.049**
• IgA (mg/dL)	167 ± 110	166 ± 73	0.363
• Hematuria [N (%)]	6 (27)	6 (24)	0.530
• Proteinuria [N (%)]	6 (27)	5 (20)	0.732
• Occult blood in stool	7 (32)	10 (40)	0.391
GIS[5] involvement	14 (64)	15 (60)	0.798
• Involvement time (week)	1.7 ± 0.7	2.2 ± 1.2	0.268
Renal involvement	12 (55)	8 (32)	0.103
• Involvement time (week)	29.5 ± 22.4	18.3 ± 16.9	0.309
• Nephritis confirmed with biopsy	4 (18)	3 (12)	0.426
Steroid treatment	14 (64)	15 (60)	0.798
Relapse	6 (27)	12 (48)	**0.029**

[1]ESR: erythrocyte sedimentation rate, [2]>20 mm/h, [3]CRP: C-reactive protein, [4]>5 mg/L, IgA: immunoglobulin A, [5]GIS:gastrointestinal system

Similarly, patients with M694V mutation had higher rate of elevated CRP and relapse rate (Table 4).

Table 4. Comparison of clinical and laboratory findings in Henoch Schonlein purpura patients without and with *M694V* mutation in *MEFV* gene.

	M694V (-) patients	M694V (+) patients	P
Female / Male	18/17	5/7	0.402
Age at diagnosis (years)	7.3 ± 2.4	8.2 ± 3.8	0.345
Preceding infection [N (%)]	13 (37)	1 (8)	0.059
Symptoms [N (%)]			
• Arthralgia / arthritis	21 (60)	8 (67)	0.488
• Abdominal pain	20 (57)	8 (67)	0.410
• Invagination	2 (6)	2 (16)	0.266
• Orchitis	2 (6)	2 (16)	0.266
• Scalp edema	0	4 (30)	**0.004**
Laboratory results			
• Hemoglobin (g/dL)	12.2 ± 1.1	12.2 ± 1.3	0.970
• Leukocytes (/mm^3)	9716 ± 2428	11.518 ± 5304	0.121
• Platelets (/mm^3)	360.583 ± 104.000	396.857 ± 153.518	0.817
• ESR[1] (mm/h)	30 ± 21	38 ± 17	0.257
• Elevated ESR[2] [N (%)]	21 (60)	10 (83)	0.141
• CRP[3] (mg/L)	33 ± 54	49 ± 44	0.304
• Elevated CRP[4] [N (%)]	24 (69)	12 (100)	**0.026**
• IgA (mg/dL)	156 ± 99	198 ± 65	0.304
• Hematuria [N (%)]	14 (40)	5 (42)	0.919
• Proteinuria [N (%)]	7 (20)	3 (25)	0.501
• Occult blood in stool	12 (34)	5 (42)	0.450
GIS[5] involvement	20 (57)	8 (67)	0.410
• Involvement time (week)	1.7 ± 0.7	2.2 ± 1.2	0.268
Renal involvement	15 (43)	5 (42)	0.608
• Involvement time (week)	24.3 ± 22.0	23.2 ± 17.9	0.925
• Nephritis confirmed with biopsy	4 (18)	3 (12)	0.254
Steroid treatment	20 (57)	9 (75)	0.324
Relapse	11 (31)	7 (58)	**0.028**

[1]ESR: erythrocyte sedimentation rate, [2]>20 mm/h, [3]CRP: C-reactive protein, [4]>5 mg/L, [5]GIS:gastrointestinal system, IgA: immunoglobulin A

The rate and type of renal involvement in relation to MEFV mutation status was shown in Table 5. Interestingly, renal involvement was more common in patients without mutation, but the difference was not significant statistically [12/22 (55%) vs 8/25 (32%), p>0.05]. Three patients homozygous for M694V mutation had no renal

involvement at all. Seven patients with severe renal involvement (nephrotic proteinuria and/or nephritic syndrome) had undergone renal biopsy. Four of these children did not have mutation. All seven patients had mesangial proliferation, but crescent formation was present in only one patient who had no MEFV mutation.

Table 5. Renal involvement regarding the presence and type of *MEFV* mutations in patients with Henoch Schonlein purpura.

	Mutation (-)	M694V homozygous	M694V heterozygous	Compound heterozygous[1]	Non-M694V heterozygous
Normal	10	3	3	2	9
Microscopic hematuria	5	0	1	1	1
Proteinuria	1	0	0	0	0
Microscopic hematuria + Proteinuria	2	0	0	1	1
Nephrotic proteinuria	1	0	1	0	0
Nephritic syndrome	3	0	0	1	1
Total	22	3	5	5	12

1 Four of these 5 patients had *M694V* mutation in one allel

DISCUSSION

The present study determined a MEFV variants prevalence of 52% in pediatric HSP patients, and this prevalence is significantly higher than the overall prevalence of MEFV variants in the healthy Turkish population (21). This high prevalence of MEFV variants in HSP patients is consistent with the results from other studies (11-19). In fact, several studies have demonstrated an increased prevalence of vasculitis in patients with FMF (7, 8). This was attributed to uncontrollable inflammation due to the altered function of the pyrin protein coded by the mutated MEFV gene (9). Half of the patients with FMF were reported to have circulating immune complexes, complement consumption, defective complement inhibition, and unregulated TNF (tumor necrosis factor) release during febrile episodes (22).

Heterozygous mutations were more common (60%) than compound heterozygous (20%) and homozygous (20%) mutations in our study population. Various studies also showed that heterozygous MEFV mutations are more prevalent in HSP patients (11,14-16,19). The most prevalent mutation in our patients was M694V, the prevalence of which is higher in the Turkish population compared to other mutations. As expected, other studies conducted in Turkey on HSP patients also identified the same mutation as the most dominant (15,16). However, studies conducted in Israel and China determined E148Q as the most prevalent mutation (43% and 85%, respectively), while V726A was the most prevalent mutation in a study from Egypt reflecting the effect of ethnic differences (14,18,19).

Approximately one half of the cases of HSP are preceded by an upper respiratory tract infection (23). Overall preceding infection rate was 30% in our patients being lower in patients with MEFV mutations than in those with no mutation (20% vs 41%). Moreover, preceding infection rate was only 8% in patients carrying M694V mutation. Autoinflammatory diseases including FMF are characterized by spontaneous attacks of inflammation cause by the dysregulation of the innate immune system

(24). Although the attacks of FMF were reported to be triggered by some factors including starvation, cold exposure, emotional stress, tiredness, and menstruation, infection was not a common triggering factor (25). The M694V mutation is known to be associated with more severe clinical phenotype in FMF, and probably patients with this mutation did not require a strong provocative stimulus like infection for triggering of inflammatory episodes such as vasculitis attack including HSP (26).

Comparison of our patients with and without MEFV mutations in terms of demographic and clinical variables did not reveal any significant difference in gender, age of onset, and joint-renal-gastrointestinal-genital involvement. Many previous studies have revealed similar results, although He et al. (18) reported an association between E148Q mutation and higher rate of joint involvement, and Bayram et al. (16) reported more prevalent genital involvement in patients with mutations in exon 10. Moreover, Bonyadi et al. (12) reported more common, albeit insignificant, joint involvement in patients with MEFV mutations. Presenting age was significantly lower in patients with MEFV mutations than in those without mutation in one study (6.9 vs 8.3 years), while it was similar in others being about 8 years (as in our patients) in all children with HSP regardless of the presence of MEFV mutations (11,13,15-17).

We found scalp edema in 30% of patients with M694V mutation, while none of the children without M694V mutation had scalp edema. Although subcutaneous edema is common in HSP (21%-52%), it is usually seen in the dependent parts of the body (27,28). Two studies from Turkey showed that patients with MEFV mutation had subcutaneous edema more frequently (13,15). According to Özçakar et al. (15) the patients with MEFV mutations, whatever the age, had high rate of edema (60%). However, their patients usually had edema in the dependent parts of the body along with arthritis and they emphasized that patients with HSP should be evaluated for FMF and MEFV mutations if they present with edema and arthritis. On the other hand, face and scalp edema are uncommon especially in children older than 2 years of age (29). As the presenting age of our patients with M694V mutation was approximately 8 years, older children with HSP who present with scalp edema should be evaluated for M694V mutation carriage. Influence of MEFV variants on laboratory parameters in HSP patients has also been evaluated in various studies. Elevated acute phase reactants like ESR, CRP and leukocytosis were reported in Turkish HSP patients with MEFV variants, specifically those in exon 10 (11,15-17). Therefore, it has been suggested that MEVF variants could affect the clinical presentation of HSP in countries where FMF is prevalent (15). The results in our study population also showed a tendency towards higher inflammation in patients with MEFV mutations in general, and in those with M694V mutation in particular.

Relapse of HSP is common and seen in up to one-third of patients being more frequent in those with renal involvement (28). In our study population, overall relapse rate was 38% being significantly higher in the group with MEFV variants (48%) and specifically in patients carrying M694V mutation (58%). Since renal involvement was not higher in the group with MEFV variants and in patients carrying M694V mutation, this increased relapse rate in these patients could not be attributed to kidney involvement. Similarly, Gershoni et al. (14) reported two-fold higher relapse rate in patients with MEFV variants. Kargin Cakici et al. (30) also reported higher relapse rate especially in patients carrying exon 10 mutations.

The overall prognosis of HSP is favorable and the long-term prognosis is usually dependent on the severity of renal involvement. The incidences of nephritis and end-stage renal disease in patients with HSP are 41-61% and 2-6%, respectively (31-33). The risk of long-term renal failure is high if the presentation is nephritic/nephrotic syndrome and/or there are >50% crescentic or sclerosing glomeruli in renal biopsy (34,35). In our study population, the overall incidence of renal involvement was 35% and was not increased in patients with MEFV variants. Furthermore, none of the three patients with homozygous M694V mutation demonstrated renal involvement. Other studies from Turkey showed that renal involvement rate was similar in patients with and without MEFV variants (and specifically with M694V mutation) and vary between 8 to 41% (11,13,15-17). The limitations of the present study are the small sample size and selective approach for MEFV mutation analysis that might affect the incidence of MEFV

mutations in the studied population, and the related clinical and laboratory data.

In conclusion, MEFV variants are more prevalent in patients with HSP compared to the healthy population; patients with MEFV variants, especially M694V mutation, had lower rate of preceding respiratory infection, higher rate of scalp edema and higher relapse rate. However, renal involvement and long-term prognosis were not affected by MEFV variants.

Conflict of Interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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