LUCRĂRI ORIGINALE

MEFV gene mutations (M694V, V726A, M680I, and A744S) in Iranian children with Henoch-Schönlein Purpura

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ABSTRACT

Introduction: *Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children. Several risk factors play important role in pathogenesis of HSP. We aimed to study the MEFV gene mutations (M694V, V726A, M680I, and A744S) in Iranian children with HSP.* ***Material and Methods:*** *50 unrelated pediatric cases were studied regarding M694V, V726A, M680I, and A744S mutations using ASO-PCR method.* ***Results:*** *24% of cases had a mutation. 22% of cases had M694V mutations. One out of 50 (2%) patients had V726A mutation. In 76% of cases no mutation was determined. In other hand, 13 out of 100 alleles (13%) were carrier for one mutation. 12 out of 100 alleles had M694V mutations (%12) and 1 out of 100 alleles had V726A mutation (%1). In 87 out of 100 alleles no mutation was detected. M680I and A744S mutations were not found in tested group. Mutation study and analysis demonstrated that the most frequent mutation was M694V (22%). Frequency of alleles were 0.12, 0.01,0,0,0.13, and 0.87 regarding M694V, V726A, M680I, A744S, total mutation, and wild type alleles, respectively. Our findings imply that M694V was dominant mutation.* ***Conclusions:*** *This report as the first investigation of its kind in Iranian Azeri Turkish patients implying that M694V mutations are more frequent in tested group in comparison with general population. So it is suggested that investigation of M694V mutations should be considered as genetic test for diagnosis of HSP among Iranian Azeri Turkish patients.*

Keywords: *MEFV gene, M694V, V726A, M680I, A744S, mutations, Iranian, HSP*

REZUMAT

Mutaţiile genelor MEFV (M694V, V726A, M680I şi A744S) la copiii iranieni cu purpura Henoch-Schönlein

Introducere: *Purpura Henoch-Schönlein (PHS) este cea mai frecventă vasculită sistemică la copii. Mai mulţi factori de risc joacă un rol important în patogeneza PHS. Ne-am propus să studiem mutaţiile genei MEFV (M694V, V726A, M680I, şi A744S) în populaţia pediatrică iraniană cu PHS.* ***Material şi Metodă:*** *50 de cazuri independente pediatrice au fost studiate în ceea ce priveşte mutaţiile M694V, V726A, M680I şi A744S folosind metoda ASO-PCR.* ***Rezultate:*** *24% din cazuri au avut o mutaţie. 22% din cazuri au avut mutaţii M694V. Unul din 50 pacienţi (2%) a avut mutaţie V726A. În 76% din cazuri, nici o mutaţie nu a fost determinată. Pe de altă parte, 13 din 100 de alele (13%) au fost purtătoare pentru o mutaţie. 12 din 100 alele au avut mutaţii M694V (12%) şi 1 din 100 de alele a avut mutaţie V726A (1%). În 87 din 100 de alele nici o mutaţie nu a fost detectată. Mutaţiile M680I şi A744S nu au fost găsite în grupul testat. Studiul mutaţiei şi analiza datelor a demonstrat că mutaţia M694V a fost cea mai frecventă (22%). Frecvenţa de alele a fost 0.12, 0.01,0,0,0.13, şi 0.87 în ceea ce priveşte mutaţia totală M694V, V726A, M680I, A744S, şi respectiv alelele de tip sălbatic. Constatările noastre arată faptul că M694V a fost mutaţia dominantă.* ***Concluzii:*** *Concluziile studiului prezent sunt că la pacienţii cu PHS a fost găsită mutaţia M694V. Se sugerează deci faptul că purtătorii genei M694V mutante, în comparaţie cu populaţia generală, pot avea mai multe şanse de a avea PHS şi analiza ei ar trebui să fie considerată ca test genetic pentru diagnosticul de PHS la copii iranieni azeri turci.*

Cuvinte-cheie: *gena MEFV, M694V, V726A, M680I, A744S, mutaţii, Iranian, PHS*

Introduction

Henoch-Schönlein purpura (HSP) is well defined as inflammatory disorder and the most usual systemic vasculitis of small vessels in children[1]. Its incidence is ranging from 10 to 20 per 100,000 children[2]. HSP is known by purpuric rash, arthralgias, abdominal pain, bleeding of gastrointestinal system, nephritis, hemorrhage of lungs, neurological problems, morbidity and mortality[2-4]. The gastrointestinal and renal systems are the typical organs involved with HSP[4]. The aetiopathogenesis of HSP is poorly understood[5,6]. Several risk factors play important role in pathogenesis of HSP[7]. Results of recent studies demonstrated that HSP is significantly associated with HLA-DRB1*018, renin-angiotensin system gene polymorphisms (ACE-I/D, M235T or T174M)[9], transforming growth factor (TGF)-β gene promoter C-509T polymorphism[10], increased levels of TNF-alpha in serum[11-14], IL-6[12-14], IL-8[15,16], TGF-β[17], vascular endothelial growth factor18, nitric oxide synthase[19], IL-1β[20], IL-1 receptor antagonist allele 2 (ILRN*2)[21], PAX2[22], HLA-B35[23], HLA-DRB1[24,25]. Approximately 142 mutations have been identified within MEFV gene[26,27]. HSP may have been associated with Familial Mediterranean fever (FMF)[28]. The prevalence of HSP is ranging from 0.05% to 0.8% in the general individuals from Turkish population[28]. Also, MEFV gene variants are supposed to be essential for HSP predisposition in Turkish population[29]. HSP was reported in approximately 5% of cases with FMF[30]. The aim of present

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Table I. Mutations and sequences of primers

Mutation	Primer	5'→3' sequence
M694V	common	tga cag ctg tat cat gtt ctg ggc tct ccg
	normal allele	tcg ggg gaa cgc tgg acg cct ggt act cat ttt cct tcc t
	mutant allele	tcg ggg gaa cgc tgg acg cct ggt act cat ttt cct tcc c
V726A	common	tgg agg ttg gag aca aga cag cat gga tcc
	normal allele	tgg gat ctg gct gtc aca ttg taa aag gag atg ctt cct a
	mutant allele	tgg gat ctg gct gtc aca ttg taa aag gag atg ctt cct g
M680I	common	tta gac ttg gaa aca agt ggg aga ggc tgc
	normal allele	att atc acc acc cag tag cca ttc tct ggc gac aga gcc
	mutant allele	att atc acc acc cag tag cca ttc tct ggc gac aga gcg
A744S	common	gag gtg gag gtt gga gac aa
	normal allele	cca gag aaa gag cag ctg gc
	mutant allele	cca gag aaa gag cag ctg ga

study was to investigate four MEFV gene mutations (M694V, V726A, M680I, and A744S) in Iranian pediatrics with HSP.

Materials and methods

A total of 50 pediatric patients with HSP (28 males and 22 females) entered the study. Patients were invited to participate within study by available telephone numbers in registry system unit of the hospital. Two pediatric specialists studied the condition of diseases and medical history information. We studied only cases that were resident in the West Azerbaijan Province of Iran. Familial and medical history, physical evaluations, and clinical tests were carried out by the same physician for all patients. All findings were evaluated by two pediatric specialists using the criteria for the classification of HSP as described previously[30,31]. Diagnosis of HSP was carried out based on the finding of three or more of the criteria proposed by Michel et al[31]. After taking an informed written consent from the parents of the children for research study of DNA, genomic DNA was isolated from 3-4 ml whole blood collected with ethylenediaminetetraacetic acid (EDTA) using 'salting out' method[32]. M694V, V726A, M680I, and A744S mutations in MEFV gene were determined using ASO-PCR method as reported by others[26,33]. Optimized primer pairs are reported in Table I. Allele-Specific Oligonucleotide PCR procedure was carried out via primary denaturation at 94° C for 9 minutes, and then followed by 35 cycles with 10 sec at 94° C, 10 sec. at 60° C and 30 sec. at 72° C. Final extension reaction was performed for 10 minutes at 72° C[26,33]. The amplified fragments as PCR products were separated and visualized by 2% agarose gel electrophoresis that is stained with ethidium bromide. The frequencies of MEFV gene mutant and normal alleles as well as genotypes were found by direct counting.

Table II. Demographic findings of studied patients with HSP

Male F (%F)	28 (56%)
Female F (%F)	22 (44%)
Male/Female	1.27
Age (years)	
Males:	ranging: 1 to 14
	mean ± SD: 6.142±3.377
Females:	ranging : 2.5 to 11
	mean ± SD: 6.25±2.524

F: Frequency

Results

Demographic findings of the studied patients with HSP were reported in table II. A total of 50 cases with a mean age ± SD of 6.19±3.003 ranging 1 to 14 years old detailing 28 (56%) males with a mean ± SD of 6.142±3.377 ranging 1 to 14 years old and 22 (44%) females with a mean ± SD of 6.25±2.524 ranging 2.5 to 11 years old were entered the study. The clinical features in the 50 HSP patients are summarized in table III. MEFV genotypes and allele frequencies among 50 Iranian Azeri Turkish patients with HSP are indicated in table IV.

Of the unrelated tested group, 12 (24%) had one mutation. Of those cases with mutations, one patient was homozygous (2%) and 10 were heterozygous for M694V mutations (20%). Also, one patient was heterozygous for V726A mutation (2%). M680I and A744S mutations were not found in tested group. Mutation study and analysis demonstrated that of the investigated alleles the most frequent mutation was M694V (22%). Frequency of alleles were 0.12, 0.01, 0, 0, 0.13, and 0.87 regarding M694V, V726A, M680I, A744S, total mutation, and wild type alleles respectively.

Discussion

HSP not only is known as the most common childhood vasculitis but also is an immunologically related disease[35]. Several risk factors have been associated with HSP and the main etiology is still unknown[35]. Infection of upper respiratory system is present in 35-52% of cases, viral and streptococcal infections trigger HSP predisposition[35-37]. Based on the infectious etiology, the HSP usually occurs in the autumn and winter seasons[38]. In HSP, immune deposits especially IgA leads to inflammation and necrosis of the arterial walls as well as erythrocytes extravasation, tissue infiltration of neutrophils and leukocytoclastic vasculities[38,39]. HSP may cause damage in wide range of tissues including skin, respiratory tract, gastrointestinal tract, renal failure, central nervous system, symmetrical muscle involvement, joints, etc.[38-43]. It has been demonstrated that HSP has been associated with Familial Mediterranean Fever (FMF)[28,44-46]. There are no definitive clinical characters and MEFV gene mutations for the association HSP-FMF[44-46]. FMF as an autosomal recessive disease is more usual among individuals of Mediterranean ancestry[47,48]. FMF is along with recurrent self-limited fever attacks and vasculitis[47,48]. Mutations within the MEFV gene result in FMF[28,47,48]. The functional product of MEFV gene, pyrin, prevents neutrophil activation or down regulates neutrophil activity for inflammation resolvation[26,48-50]. Recent reports

Table III. Clinical features in 50 HSP patients

Character	Total (%)	Males (%)	Females (%)
Arthritis	47 (94)	27 (57.45)	20 (42.55)
Abdominal pain	42 (84)	22 (52.38)	20 (47.62)
Gastrointestinal bleeding	10 (20)	6 (60)	4 (40)
Fever	13 (26)	12 (92.31)	1 (7.69)
Intussusceptions	2 (4)	1 (50)	1 (50)
Vertigo	1 (2)	1 (100)	0 (0)
Scrotal edema	1 (2)	1 (100)	0 (0)
Skin Necrosis	1 (2)	0 (0)	1 (100)
Appendectomy	2 (4)	1 (50)	1 (50)
Relapse of HSP disease	12 (24)	5 (41.67)	7 (58.33)
Proteinuria	21 (42)	7 (33.33)	14 (66.67)
Nephrotic proteinuria	4 (8)	2 (50)	2 (50)
Hematuria	17 (34)	8 (47.06)	9 (52.94)
Hypertension	2 (4)	1 (50)	1 (50)
Rapidly progressive glomerulonephritis	2 (4)	1 (50)	1 (50)
Treatment with corticosteroids	39 (78)	26 (66.67)	13 (33.33)
Response of HSP complications to corticosteroids	27 (54)	18 (66.67)	9 (33.33)
Treatment with other immunosuppressive	12 (24)	5 (41.67)	7 (58.33)

indicate that the mutated MEFV allele may be acting as a susceptibility factor and favor the development of severe vasculitis in some rheumatic diseases including HSP[50,51]. Production of un-functional pyrin because of mutation in MEFV gene has important role in up regulation of the inflammatory responses which favors MEFV mutant carriers to develop HSP or other related disorders[46,48,51,52]. According to the study, one patient was diagnosed to be homozygous and 10 patients were diagnosed to be heterozygous for M694V mutation. Also, one patient was diagnosed to be heterozygous for V726A mutation (2% of cases). Based on the results of Bonyadi et al (2010) regarding MEFV gene mutations in Iranian Azeri Turkish general population (the same population in our study) which showed no carriers for M694V, M694I, and M680I[34], our findings imply that M694V was the dominant mutation in HPS patients studied. Even though M694V was the most common mutation in the Azeri Turkish FMF patients (28%)[53], it was not detected in the general population sample by Bonyadi[34]. So it is suggested that M694V mutant carriers in comparison with general population may have more chance to HPS.

Table IV. MEFV genotypes and allele frequencies among 50 Iranian Azeri Turkish pediatrics with HSP

A. Genotype		
Allele 1	**Allele 2**	**Number of cases**
M694V	M694V	1
M694V	Wild type	10
V726A	V726A	0
V726A	Wild type	1
M680I	M680I	0
M680I	Wild type	0
A744S	A744S	0
A744S	Wild type	0
Wild type	Wild type	38
Total		50
B. Allele frequencies		
Mutation	**Number of alleles**	**Frequency of alleles**
M694V	12	0.12
V726A	1	0.01
M680I	0	0
A744S	0	0
Total mutation	13	0.13
Wild type	87	0.87
Total	100	1

Conclusion

This report is the first investigation of its own kind in Iranian Azeri Turkish patients showing that M694V mutation is more frequent in tested group in comparison with general population. So, it is suggested that investigation of M694V mutation should be considered as genetic test for diagnosis of HSP among Iranian Azeri Turkish patients.

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Declaration of interest

The authors report no conflicts of interest.

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