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Mediterranean fever gene mutations in patients with idiopathic mesangial proliferative glomerulonephritis

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ABSTRACT

Background: Familial Mediterranean Fever (FMF) is the most common inherited autoinflammatory disease. Kidney involvement in FMF is usually attributed to secondary amyloidosis. Non-amyloid glomerular involvement has also been reported.
Objectives: We suppose that heterozygous mutation of Mediterranean fever (*MEFV*) gene could be the underlying cause in some cases of mesangial proliferative glomerulonephritis (MePGN) in FMF endemic area.
Materials and Methods: This prospective study was done between 2013 and 2015 in North-West of Iran among the Azari-Turkish population. A panel of *MEFV* gene including M680I, R761H, M694V, R408Q, E148Q, A744S, F479L, P369S, V726A, M694I, and E167D were studied in a group of patients with idiopathic MePGN. Clinical characteristics and therapeutic responses were compared between those with and without a mutation. A total of 39 idiopathic MePGN patients and 156 healthy subjects were studied.
Results: Heterozygote mutations of *MEFV* gene were detected in 11/39 (28.2%) of MePGN patients and 46/156 (17.3%) of controls. Clinical response regarding 24 hours urine protein excretion was significant in mutation-negative patients after 6 months of follow-up.
Conclusions: This study shows a possible underlying role of heterozygous *MEFV* gene mutation in the clinical course of some case of idiopathic MePGN, particularly in FMF endemic population.

Implication for health policy/practice/research/medical education:
In the present study we aimed to examine the impact of a panel of *MEFV* gene (M680I, R761H, M694V, R408Q, E148Q, A744S, F479L, P369S, V726A, M694I, and E167D) polymorphisms on patients with mesangial proliferative glomerulonephritis. In patients with MePGN and heterozygous mutations of *MEFV* gene, a lower therapeutic response was observed. Combination therapy with antiproteinuric treatment is suggested to be a valuable therapeutic strategy in MEFV positive mutation- MePGN patient.

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Original Article

1. Background

Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by transient febrile episodes accompanied by abdominal and chest pain, arthralgia, myalgia, arthritis, and skin rash symptoms (1). Mediterranean fever gene (*MEFV*) is localized on the short arm of chromosome 16 and encodes a 781-amino-acid protein known as pyrin (2). FMF is also known as an autosomal recessive condition prevalent in Armenian, Turkish, and Arab populations. Renal involvement in FMF is usually attributed to secondary amyloidosis. Additionally, because of its

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auto-inflammatory nature, non-amyloid glomerular involvement has been described in some cases of FMF in literature, including mesangial proliferation glomerulonephritis (MePGN) with IgA or IgM deposit, focal or diffuse proliferative glomerulonephritis (GN), membranoproliferative GN and vasculitis with rapidly progressive glomerulonephritis (RPGN) renal course (3-7). MePGN is a diffuse expansion of mesangial cells or matrix. It has different etiologies with highly variable clinical courses. Patients with MePGN and dominant IgA or IgM deposits are known as IgA or IgM nephropathy consequently (8). In this cohort, the *MEFV* gene mutations were studied in a group of patients with idiopathic MePGN. Then clinical characteristics and the therapeutic response were compared between those with and without a mutation.

2. Objectives

We suppose that heterozygous mutation of Mediterranean fever (*MEFV*) gene could be the underlying cause in some cases of mesangial proliferative glomerulonephritis (MePGN) in FMF endemic area.

3. Materials and Methods

3.1. Patients selection

This prospective study was conducted in Kidney Research Center of Tabriz University of Medical Sciences from April 2013 to April 2015. The eligibility for inclusion criteria was all patients with light microscopy diagnosed MePGN, according to the WHO criteria (9) with negative immunoglobulin (Ig) deposition in immunofluorescence (IF) study (10). Patients whose IF findings were consistent with IgA nephropathy, IgM nephropathy, C1q nephropathy, or presence of prominent C3 deposits, were excluded.

Patients with systemic diseases such as active hepatitis, diabetes mellitus, malignancy, systemic lupus erythematosus (SLE), Henoch-Schonlein purpura, and mixed connective tissue disease were excluded from the study (11). Complete remission (CR) was defined as proteinuria decrement below 500 mg/24 hours. Partial remission was considered as 50% decrease from baseline. No responders did change their protein excretion (10). We did not find enough literature to support our presumption that heterozygote FMF gene mutation without any clinical sign of FMF could be a possible cause for mesangial involvement; hence we did not start colchicine for these patients at the start. All patients received angiotensin receptor blockers and/or angiotensin converting enzyme inhibitors. Those with nephrotic range proteinuria at first received corticosteroid (1 mg/kg, for 8-12 weeks and then on tapering course). In non-responders, cyclosporine (2 mg/kg) was added to the therapeutic regiment. All patients were under regular nephrology clinic visit and proteinuria measurement for at least 6 months.

3.2. Gene study

Genomic DNA from peripheral blood leukocytes was extracted according to Miller et al protocol (12). Five common mutations including M680I (G to C transversion), E148Q, M694V, M694I, and V726A were studied using PCR and PCR-restriction fragment length polymorphism (RFLP) approaches as described previously (12-15). For each test, proper positive and negative controls were used and the positive results were repeated in order to confirm the reproducibility. PCR and RFLP products were electrophoresed on an agarose gel (2%). Furthermore, patients with non-mutated allele(s) were examined for less common mutations including p.R408Q (c.1223G>A), p.E167D (c.501G>C), p.F479L (c.1437C>G), p.P369S (c.1105C>T), p.A744S (c.2230G>T) and p.R761H (c.2282G>A) based on the study of Medlej-Hashim et al (16). Accordingly, suitable positive and negative controls were used and the positive results were repeated in order to confirm the reproducibility.

3.3. Ethical issues

The research followed the tenets of the Declaration of Helsinki. Our study protocol was approved by the ethics committee of Tabriz University of Medical Sciences (ethics code# IR.tbzmed.REC.1393.218). This study was conducted as the internal medicine residential thesis of Taraneh Majidi. The patients' medical records were used for data gathering and this process was secret.

3.4. Statistical analysis

Data analyzed was performed by analysis of variance (ANOVA) test and individual post-test comparisons were made for comparisons of interest and when the interaction was significant ($P < 0.1$). Comparison of quantitative variables between the two groups was tested using Mann-Whitney U test. Qualitative variables were tested by the chi-squared test. Statistical analysis was performed using the IBM SPSS software version 17.0. *P* value of <0.05 was statistically considered as significant.

4. Results

Demographic, clinical and laboratory characteristics of the studied patients (M/F: 22/17, mean age of 40.13±14.42, range; 16-57 years), have been shown in

Table 1. Heterozygote mutations of *MEFV* gene were more common among MePGN than controls (patients 11/39, 28.2%) versus (controls 46/156, 17.3%), but the difference was not significant ($P=0.12$, Table 2). There was not a significant difference between mutation negative- MePGN and mutation positive – MePGN patients regard to their entry 24 hours urine protein excretion (Table 3). However, after treatment and 6 months of follow-up complete response happened in the majority of mutation negative- MePGN compared to positives ($P=0.01$, Table 4).

5. Discussion

We found that patients with MePGN and heterozygous mutations of *MEFV* genes had a lower therapeutic response in terms of proteinuria compared to MePGN

Table 1. Demographic and clinical data in 39 patients with MePGN

N	Age	Sex	Creatinine (mg/dL)			Proteinuria (mg/24h)			Extra renal presentation	Renal presentation	Treatment			MEFV gene mutations heterozygous
			Base	3 mon	6 mon	Base	3 mon	6 mon			ACE-I	Pred	Cyclo	
1	47	M	1.2	1.2	0.8	9711	7927	5167	Edema	Proteinuria	+	+	+	-
2	42	M	0.9	0.6	0.9	2836	2416	2470	Edema	Proteinuria	+	+	+	-
3	27	M	1.1	0.9	0.7	4500	2900	2010	Edema	Proteinuria	+	+	+	F479L, E167D
4	36	M	1.1	1.1	1.1	5750	55	100	Edema	Proteinuria	+	+	-	-
5	60	M	0.9	0.9	1.0	3201	2249	1040	Edema	Proteinuria hematuria	+	+	+	-
6	61	F	7.4	0.9	0.9	4500	57	104	Edema	AKI, Proteinuria	+	+	-	-
7	26	F	0.9	0.9	0.7	3333	4500	2089	Edema	Proteinuria	+	+	+	E148Q
8	33	F	0.6	0.5	0.6	2937	800	1450	Edema	Proteinuria	+	+	-	-
9	60	M	1.6	1.8	1.6	3683	800	1461	Edema	Proteinuria	+	+	-	E148Q
10	45	M	1.7	3.7	2.3	4500	3410	4784	Edema	Proteinuria	+	+	+	-
11	43	M	0.7	1.1	0.7	1540	153	132	Edema	Proteinuria	+	+	-	-
12	37	M	1.2	1.0	1.0	1717	714	40	Edema	Proteinuria	+	+	-	-
13	19	M	2.8	0.9	0.9	2800	200	93	Sever Edema	AKI/Proteinuria	+	+	-	V726A
14	27	F	0.8	0.8	0.8	3632	66	66	DVT, Edema	Proteinuria	+	+	-	-
15	34	F	0.9	0.8	0.8	3000	800	371	Edema	Proteinuria	+	+	-	-
16	45	M	1.2	1.1	0.8	2888	1025	580	Edema	Proteinuria	+	+	-	-
17	24	F	0.9	0.7	0.7	3500	507	604	Edema	Proteinuria	+	+	-	-
18	61	M	1.0	1.2	1.2	4438	398	264	Edema	Proteinuria	+	+	+	-
19	38	F	0.6	0.6	0.8	5358	4500	2500	Edema	Proteinuria	+	+	+	-
20	44	M	0.8	1.0	1.0	4000	2208	480	Edema	Proteinuria	+	+	+	-
21	33	M	0.7	1.3	1.3	2650	2669	206	Edema	Proteinuria	+	+	+	-
22	41	M	0.9	1.4	1.1	9552	4420	7173	Intractable edema	Proteinuria	+	+	+	E148Q
23	31	M	1.0	0.9	0.9	4396	3767	2550	Edema	Proteinuria	+	+	+	E148Q
24	39	F	0.8	1.0	1.2	1823	2522	3060	Edema	Proteinuria	+	+	+	-
25	20	F	1.1	1.0	1.0	2110	1068	409	Edema	Proteinuria	+	+	-	A744S
26	24	F	0.8	0.7	0.8	4500	1000	800	Edema	Proteinuria	+	+	-	-
27	62	F	1.4	2.8	1.7	4500	4500	3726	Edema	Proteinuria	+	+	+	E148Q
28	75	F	2.1	1.6	1.7	3123	1435	1150	Edema	Proteinuria	+	+	-	E148Q
29	54	M	1.4	1.3	1.4	1800	6653	3888	Edema	Proteinuria	+	+	+	E148Q
30	64	F	1.4	3.2	2.3	3795	3846	7428	Arthritis, Edema	AKI, Proteinuria	+	+	+	P369S
31	53	M	1.6	1.7	1.6	8000	3000	4500	Edema	Proteinuria	+	+	+	-
32	42	M	1.2	1.0	1.2	8000	1123	157	Edema	Proteinuria	+	+	-	-
33	40	F	1.0	0.8	0.8	1800	853	336	Edema	Proteinuria	+	+	-	-
34	25	M	1.3	1.0	0.9	9599	569	312	Edema	Proteinuria	+	+	-	-
35	39	F	0.8	0.9	0.7	4500	1983	130	Edema	Proteinuria	+	+	-	-
36	37	2	0.6	0.7	1.0	9750	1182	431	Edema	Proteinuria	+	+	-	-
37	16	M	0.6	0.6	0.8	8000	2000	400	Edema	Proteinuria	+	+	-	-
38	43	M	1.9	1.7	1.8	8000	4200	4500	Edema	Proteinuria	+	+	+	-
39	18	F	0.8	0.8	0.8	4504	150	150	Edema	Proteinuria	+	+	-	-

Abbreviations: MePGN, mesangioproliferative glomerulonephritis; ACE, angiotensin converting enzyme inhibitor; MEFV, Mediterranean fever; Pred, prednisolone; Cyclo, cyclosporine; AKI, acute kidney injury; DVT, deep vein thrombosis.

Table 2. Distribution of *MEFV* gene mutations in MePGN patients and controls

Mutation	Group	
	Patient (n=39)	Control (n=156)
M694V	0(0)	0(0)
M680I	0(0)	0(0)
E148Q	7(17.9)	45 (28.8)*
R761H	0(0)	0(0)
R408Q	0(0)	0(0)
A744S	1(2.6)	0(0)
F479L	1(2.6)	0(0)
M694I	0(0)	0(0)
V726A	1(2.6)	1(0.6)
P369S	1(2.6)	0(0)
E167D	1(2.6)	0(0)

Abbreviations: MEFV, Mediterranean fever; MePGN, mesangial proliferative glomerulonephritis.
*$P = 0.17$

Table 3. Serum creatinine and 24 hours urine protein excretion in different time intervals in MePGN patients with or without *MEFV* gene mutation

Variables	Time	Mutation		*P**	*P***
		Positive (n=11)	Negative (n=28)		
Cr (mg/dL)	Base	1.4 (1.0-1.6)	0.9 (0.8-1.2)	0.01	
	3 mon	1.3 (0.9-1.8)	0.95 (0.7-1.1)	0.02	0.10
	6 mon	1.1 (0.9-1.7)	0.9 (0.8-1.1]	0.11	
Urine Pr (mg/24 h urine)	Base	3683 (2800-4500)	4438 (2888-8000)	0.42	
	3 mon	3767 (1068-4500)	1074 (522-2495)	0.02	0.007
	6 mon	2089 (1150-3888)	415 (151-2215)	0.02	

Abbreviations: MePGN, mesangio proliferative glomerulonephritis; Cr, serum retaining; Pr, protein; MEFV, Mediterranean fever.
Data are shown with Median (Min-Max).
** Within group; *** Between group.

Table 4. Proteinuria response in MePGN patients with and without MEFV gene mutation

Mutation	Response			*P* value
	No Response	Partial Response	Complete Response	
Negative, No. (%)	4 (14.3)	5 (17.9)	19 (67.9)	0.01
Positive, No. (%)	6 (54.5)	3 (27.3)	2 (18.2)	

Abbreviations: MePGN, mesangio proliferative glomerulonephritis; MEFV, Mediterranean fever.

patients without a mutation. Heterozygous mutation of E148Q was the most common mutation in our patients and also controls. In concordance with our results, heterozygous E148Q mutation has been reported among 12% of the Turkish population, 10% of Ashkenazi Jews, and up to 20% of our Iranian-Azari population (17-20). FMF is an autosomal recessive disorder, but the frequent discovery of clinical phenotype among patients with heterozygous mutations of *MEFV* gene suggested that the disease might be transferred as an autosomal dominant trait in some instances (21,22). Secondary amyloidosis is the main cause of renal involvement, however, various types of glomerulonephritis including MePGN have been reported in FMF patients (23-26). In a large report on 101 FMF patients, 12.3% had amyloidosis renal involvement, and 21.7% had non-amyloid renal lesions, including various types of glomerulonephritis (23). The association between FMF and IgA nephropathy has been described previously (5). The association between the clinically silent heterozygous mutation of *MEFV* gene and renal involvement is not too much discussed (24). IgA nephropathy is the prototype of MePGN. Secondary MePGN is documented in a variety of disorders, such as systemic lupus erythematosus, Henoch-Schönlein purpura, rheumatoid arthritis, and vasculitic syndromes (27-29). Therapeutic response to corticosteroid and colchicine has been reported in a few patients with MePGN who harbored heterozygous *MEFV* gene mutations (3,4,24,26). *MEFV* gene mutations upregulate the inflammatory cytokines including interleukin-1b and nuclear factor kappa B that may enhance the glomerular inflammation (6,26,30).

6. Conclusions

The results of our study indicated the possible underlying role of heterozygous *MEFV* gene mutation in the clinical course of some case of idiopathic MePGN, particularly in an endemic area. Therapeutic strategy in patients with MePGN and heterozygous *MEFV* gene mutation is still obscure. Addition of colchicine to their antiproteinuric therapy could be a useful suggestion (4). Further studies with large populations are needed to explain the significance of the studied mutations on clinical progression of glomerulonephritis.

Study limitations

A small sample size due to the low incidence of the MePGN is our limitation in the present study.

Authors' contribution

JE, TM and RM contributed to the design of the research and analyzed the data. MB conducted the experiments. SZ and MRA prepared the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors report no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication,

double publication) have been completely observed by the authors.

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