Familial Mediterranean Fever, Polyarteritis Nodosa and MEFV Mutations

Ailevi Akdeniz Ateşi, Poliarteritis Nodosa ve MEFV Mutasyonları

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ABSTRACT

OBJECTIVE: The aim of this study was to perform a systematic review of the relevant literature aiming to assess the role of MEFV mutations on FMF-associated PAN.

MATERIAL and METHODS: We conducted a comprehensive review of the literature with an attempt to analyze cumulated data regarding the role of MEFV mutations in the development of FMF-associated PAN.

RESULTS: We found a total of 96 cases with FMF and PAN. MEFV mutations were available only in 28 patients of whom 26 have been reported from Turkey. Twenty-five (89 %) of the 28 patients had at least one M694V allele and 13 (46%) of them had the homozygous M694V genotype.

CONCLUSION: Since M694V is accepted to be associated with more severe inflammation as compared to other mutations, one can speculate that this enhanced inflammation may predispose to PAN and MEFV mutations and probably contribute to the risk of developing PAN in areas where FMF is endemic. In addition, MEFV mutations, particularly M694V, might be searched in patients from certain ethnic groups, especially in young patients having PAN without any predisposing disease.

KEY WORDS: Familial mediterranean fever, M694V, MEFV, Polyarteritis nodosa, Renal involvement

ÖZ

AMAÇ: Bu çalışmanın amacı, ilgili konuda MEFV mutasyonlarının ile AAA ilişkili PAN üzerindeki rolünü sistematik bir gözden geçirme yaparak değerlendirmektir .

GEREÇ ve YÖNTEMLER: MEFV mutasyonlarının ile AAA ilişkili PAN gelişimindeki rolünü anlamak amacı ile ayrıntılı bir literatür taraması yaptık.

BULGULAR: AAA ile ilişkili toplam 96 PAN vakası bulduk. MEFV mutasyonları sadece 26'sı Türkiye'den 28 hastada vardı. 28 hastanın 25'inde (%89) en az bir M694V alleli vardı. 13 hasta ise homozigot M694V genotipi idi.

SONUÇ: M694V diğer mutasyonlara kıyasla daha şiddetli inflamasyonla ilişkili olduğu için, bu artmış inflamasyonun PAN'a yatkınlık hazırlayacağı ve MEFV mutasyonlarının AAA'nin endemik olduğu bölgelerde PAN gelişimine muhtemelen katkıda bulunabileceği düşünülebilir. Ayrıca, MEFV mutasyonları, özellikle M694V, belli etnik gruplarda, özellikle herhangi bir yatkınlaştırıcı hastalığı olmayan genç PAN hastalarında araştırılabilir.

ANAHTAR SÖZCÜKLER: Ailevi akdeniz ateşi, M694V, MEFV, Poliarteritis nodosa, Böbrek tutulumu

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INTRODUCTION

Familial Mediterranean Fever (FMF) is the most common autoinflammatory disease in the world. Amyloidosis is the most common and devastating complication of FMF, but polyarteritis nodosa (PAN), Henoch-Schonlein purpura (HSP), and glomerulonephritis can lead to important morbidity and renal problems as well, albeit rare (1-4). FMF is associated with mutations in a gene called MEFV (from MEditerranean FeVer) gene, identified in 1997. Up to now more than 200 different mutations (5) have been described in the MEFV gene and the phenotypic expression of the disease varies from one patient to another (4, 6).

A number of associations have already been studied for the development of renal amyloidosis in FMF patients including MEFV mutations (7). The data regarding the association of MEFV mutations with nonamyloid renal diseases and vasculitis such as PAN and HSP is limited (8-9). The prevalence of MEFV mutations in patients with PAN without any symptoms of FMF was analyzed to test the hypothesis of whether alterations in the MEFV gene were a susceptibility factor for the development of PAN (10). In this study, eleven of the 29 patients (38%) were found to carry MEFV mutations with the M694V allele being the most common: M694V/M694V (n=3), M694V/- (n=3), V726A/E148Q (n=1), E148Q/- (n=2), M680I/- (n=1), and K695R/- (n=1). The aim of this study was to perform a systematic review of the relevant literature aiming to assess the role of MEFV mutations on FMF-associated PAN.

METHODS

We conducted a comprehensive review of the literature in an attempt to analyze cumulated data regarding the role of MEFV mutations in the development of FMF-associated PAN. We performed the search in databases, PubMed, Web of Science, Cochrane, and local Turkish, using the terms (1) familial Mediterranean fever and polyarteritis nodosa, (2) familial Mediterranean fever and microscopic polyangiitis (MPA), and (3) familial Mediterranean fever and vasculitis without time limitation in December 2011. We also extracted abstracts from conference proceedings. Pertinent articles quoted as references in the identified papers were also reviewed. The patients published twice or thrice were included only once.

RESULTS

We found a total of 96 cases with FMF and PAN. The Turkish FMF Study Group published 24 cases with FMF and PAN in 2005 (1); however, since some of these patients were probably included in the data published previously, we did not add these 24 patients to the 96 patients. MEFV mutations were available only in 28 patients (Table I) (2,3,11-27) of whom 26 had been reported from Turkey (2,3,11-14, 16-25, 27). Twenty-five (89 %) of the 28 patients had at least one M694V allele and 13 (46%) had the homozygous M694V genotype.

In patients with PAN and FMF, there were certain specific features such as the overlap of microscopic polyangiitis and classic PAN, younger age at onset, tendency to perirenal hematoma and better prognosis. Polyarteritis nodosa was diagnosed in five patients before the diagnosis of FMF. However, symptoms associated with FMF were present in these patients except one who was an infant. Three patients had another type of vasculitis (13, 25, 27) along with PAN as well: HSP (n=1), Behçet's disease (n=1) and Kawasaki disease (n=1). All of the three patients had M694V mutations: M694V on one allele in two and homozygous M694V in one.

DISCUSSION

Polyarteritis nodosa is a systemic vasculitis that affects medium-sized muscular arteries. Unlike classical PAN, MPA is a separate ANCA-associated vasculitis affecting small vessels. The kidneys, skin, joints, muscles, nerves, and gastrointestinal tract are commonly involved in PAN. Most cases of PAN are idiopathic, although hepatitis B virus infection, hepatitis C virus infection, and hairy cell leukemia are predisposing factors in some cases.

The first international and multicenter study of patients with FMF and PAN was published in 2001 (2). The authors suggested that PAN developed at an earlier age in patients and had some overlapping features with MPA in that glomerular involvement accompanied mid-size artery vasculitis in some patients (2). This study (2) consisted of 17 patients and MEFV mutations were available only in six of them. Since then, screening for MEFV mutations and their role in various rheumatologic diseases has progressed considerably due to the development of new analysis methods, widespread use of these methods by many centers and the description of phenotype III disease, asymptomatic patients in spite of having at least two MEFV mutations (4).

Table I: MEFV mutations of 28 patients with FMF and PAN.

Genotype	n	Reference no*
Two M694V		
M694V/M694V	13	2,15,17-19,21,22,27
One M694V		
M694V/-	7	2,11-14,19,24,25
M694V/V726A	3	11,12,16,19
M694V/M680I	2	2,20
M694V absent		
E148Q/E148Q	1	26
Other	2	19, 23
Total	28	

* References 2,3,11-14, 16-25, 27 have been reported from Turkey

This is the first systematic review of the MEFV mutations in FMF patients who develop PAN. Even though at least 96 cases with FMF and PAN have been reported so far, MEFV mutation analysis was available in 28 of them. Twenty-five (89 %) of the 28 patients had at least one M694V allele. Nationwide surveys from two countries, Turkey and Armenia, included 24 and 23 (1, 28) patients with FMF and PAN, respectively. However, these studies did not report MEFV mutations of PAN patients.

The findings of the present report indicated that the M694V allele might be a risk factor for PAN in FMF. The study of Erdogan et al. (29) confirmed the role of the M694V genotype in FMF-associated PAN. They demonstrated the association between M694V mutations in FMF and vasculitis among 29 patients, 24 HSP and 5 PAN. Mutation analysis was available only in 12 patients (M694V/M694V in 10, M694V/M680I in 1, and M694V/- in 1). The authors did not specify the association between MEFV mutations and the type of vasculitis in these 12 patients.

Since patients having homozygous M694V mutation had higher disease severity scores (7), the association between the M694V allele and PAN was not surprising. Homozygous M694V mutation was also associated with amyloidosis, resistance to colchicine treatment, and central nervous system involvement in FMF (7). Moreover, protracted febrile myalgia, a feature of FMF that should be included in the differential diagnosis of PAN, seems to be associated with M694V mutations as well (30).

Another very interesting feature of the patients with FMF and PAN is the occurrence of another vasculitis in these patients: HSP, Kawasaki or MPA. This is a unique feature. Further studies will show the role of MEFV mutations for the co-existence of two vasculitides.

Our study had certain limitations: (i) The number of patients was small; (ii) It was based on published cases; (iii) The diagnoses of FMF and PAN were not interrogated; (iv) MEFV mutations were not studied in all cases; and (v) A control group was not available. Although 96 cases with FMF-associated PAN was been reported from many countries such as Armenia, Israel, England, Lebanon and Switzerland (2, 26, 28, 31-32), MEFV mutations were known only in 28 cases. Interestingly 26 of these 28 patients were reported from Turkey (2,3,11-14, 16-25, 27). The distribution of MEFV mutations among those 26 patients was two M694V mutations (n=12, 46%), one M694V mutation (n=12, 46%), and no M694V mutations (n=2, 8%) (Table). The frequencies of homozygous M694V genotype were 28% and 25% in two major Turkish studies consisting of more than 1000 FMF patients (1, 7). If these studies were presumed as control groups and the frequency of homozygous M694V genotype was compared by the Chi-Square test, there would be a statistically significant difference ($p < 0.05$) for both comparisons.

Given the rarity of FMF-associated PAN, these limitations were acceptable and had some explanations. Analysis of MEFV mutations is not a diagnostic criteria for FMF. Some cases were reported before the identification of MEFV genes. Despite lack of an actual control group, the high frequency of M694V mutations supports the role of this mutation in the pathogenesis of FMF-associated PAN.

In conclusion, since M694V is accepted to be associated with more severe inflammation as compared to other mutations, one can speculate that this enhanced inflammation may predispose to PAN and MEFV mutations and probably contribute to the risk to develop PAN in areas where FMF is endemic. In addition, MEFV mutations, particularly M694V, might be searched in patients from certain ethnic groups, especially in young patients having PAN without any predisposing disease.

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