Are carriers for *MEFV* mutations "healthy" ?

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ABSTRACT

Objective. *We aimed to compare whether carriers for the* MEFV *mutations display an increase or decrease in certain features. We compared the frequency of a number of inflammatory symptoms and diseases in carriers and a control population.*

Methods. *A questionnaire was designed to be applied to parents of children with FMF and a control group of parents. Clinical features and some diseases including the frequency of febrile episodes, abdominal pain, arthralgia, prophylaxis with penicillin, acute rheumatic fever, rheumatoid arthritis, vasculitis, spondyloarthropathy, urinary tract infection, asthma, allergy, irritable bowel disease, appendectomy and tonsillectomy were inquired. 676 parents of 440 children with FMF were surveyed in this study. Controls (n: 774) were selected as parents of healthy children.*

Results. *The presence of febrile episodes more than four per year, arthralgia, past diagnosis for acute rheumatic fever, rheumatoid arthritis and prophylaxis of penicillin, acute rheumatic fever, and rheumatoid arthritis were significantly higher in asymptomatic parents for the* MEFV *mutations compared to controls. The frequency of allergy was found to be significantly lower in the asymptomatic parents as compared to controls. There was no significant difference at the frequency of urinary tract infection and tonsillectomy between the parents of the patents and controls.*

Conclusions. *We suggest that one MEFV mutation may indeed be conferring a heightened inflammation as suggested by the increased frequency in inflammatory symptoms. The carrier status for* MEFV *mutations seem to be unique, in that they cause an alteration in the state of "health".*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory attacks of the serosal membranes (1). The Mediterranean fever (*MEFV*) gene, encodes a protein called pyrin and more than 30 mutations in this gene cause the disease (2). Carrier rate of this disease is very high, ranges varies from 1/6 to 1/3 (2-5).

FMF carriers have relatively high acute phase response although there are contradictory results in the literature (6-8). It has been hypothesized that these carriers may have susceptibility to certain symptoms or even diseases. Kogan *et al*. (9) reported that the prevalence of frequent febrile episodes was higher in heterozygotes for FMF than in healthy controls (9).

In the present study, we examined whether carriers for the *MEFV* mutations display a certain phenotype and whether they had an increase or decrease in certain features when compared to the population. We compared the frequency of numerous diseases and symptoms some related to FMF and some not, in carriers and in a control population.

Material and methods

We accepted that the parents of patients with definite FMF were obligate carriers for a *MEFV* mutation. Inclusion criteria for the study group were to be a parent of a definite FMF patient. Parents who had typical FMF symptoms or a diagnosis of FMF were excluded for the study. 676 parents of 440 children with FMF aged between 25 and 78 years (mean ± SD: 40.6 ± 8.3 years) were surveyed. Of the parents 346 (51%) were female. A genetic analysis was possible in 53 % of these patients. The parents could not be studied genetically because of financial reasons.

Diagnosis of FMF was made according to defined criteria (1) and response to colchicum. The control group (n: 774) were selected as parents of children visiting for a routine vaccination or out-patients without rheumatic diseases who had no family history of FMF. Their mean age was 40.5 ± 7.8 years, 371 (48%) was female.

All subjects were interviewed with a questionnaire. The questionnaire included questions from childhood to present time, including questions related to certain clinical features including the frequency of febrile episodes, arthralgia, abdominal pain and allergy. Participants were also requested to answer for any current or past medical history of acute rheumatic fever (ARF), rheumatoid arthritis, vasculitis, spondyloarthropathy, urinary tract infection, asthma, irritable bowel disease, appendectomy, tonsillectomy and use of penicillin prophylaxis.

A p value < 0.05 was considered statistically significant. For statistical analysis, chi-square was used.

Results

There were certain differences in the frequency of certain features and symptoms between the asymptomatic parents and control subjects (Table I). The presence of febrile episodes more than four per year, arthralgia, acute rheumatic fever, and rheumatoid arthritis were significantly higher in asymptomatic parents for the *MEFV* mutations compared to controls. In addition, the history of acute rheumatic fever, rheumatoid arthritis and prophylaxis of penicillin were significantly more common in the carriers. On the other hand the frequency of allergy was found to be significantly lower in the asymptomatic parents as compared to controls. There were no differences regarding to urinary tract infection, spondyloarthropathy, vasculitis, rheumatic carditis, asthma, appendectomy, tonsillectomy and irritable bowel disease.

In those whom a mutation analysis was available, the allele distribution revealed 65% M694V, 16%, M680I, 12% V726A, and 7% E148Q. However, comparisons were not possible since the parents were not genotyped.

Table I. Relationship between certain symptoms/diseases in the FMF gene carrier.

Symptoms/diseases	FMF gene carriers		Healthy controls		
	Number of patients	%	Number of patients	%	p
Febrile episodes (> 4 per year)	92	13.6	77	9.9	0.038
Abdominal pain	71	10.5	45	5.8	0.001
Arthralgia	160	23.7	135	17.4	0.003
Prophylaxis with penicillin	49	7.2	35	4.5	0.027
Acute rheumatic fever	22	3.3	13	1.7	0.05
Rheumatoid arthritis	19	2.8	9	1.2	0.023
Vasculitis	4	0.6	1	0.1	0.134
Spondyloarthropathy	4	0.6	4	0.5	0.848
Urinary tract infection	8	1.2	7	0.9	0.600
Asthma	19	2.8	18	2.3	0.359
Allergy	57	8.4	90	11.6	0.044
Irritable bowel disease	13	1.9	11	1.4	0.455
Appendectomy	39	5.8	41	5.3	0.695
Tonsillectomy	33	4.9	34	4.4	0.658

FMF: Familial Mediterranean fever.

Discussion

The description of the advantage described for sickle cell trait brought up the logical suggestion that "mutations" common in a given group might have been selected over ages because they conferred an advantage (10). With carrier rates as high as 1/5 the same question has come up with FMF (11). It has been suggested that *MEFV* mutations enabled a heightened inflammatory response that might have been beneficial for fighting the microorganisms or a specific organism (11). It has also been concluded that the genetic change may enhance carriers' ability to withstand certain infections (9). On the other hand, it was suggested that enhanced inflammation might predispose the carriers to some chronic inflammatory conditions. Indeed, certain features have been recognized to be different among the FMF carriers as compared to the non-carrier population. Kogan *et al.* (9) studied 521 Jews and found that febrile episodes were markedly increased in carriers as compared to non-carriers of a mutation in the FMF gene. In our study, we also found that frequency of febrile episodes over four per year was higher in heterozygotes for the *MEFV* mutations as compared to the control group. Along with fever, symptoms such as arthralgia and abdominal pain were also higher in the asymptomatic parents, who were accepted as carriers for the *MEFV* mutations, as compared to the control group. Furthermore these individuals had an increased rate of RA. This may well be explained with subclinic inflammation in the heterozygotes for MEFV mutations. Tunca *et al.* (7) demonstrated that MEFV carriers had significantly higher C-reactive protein (CRP) and serum amyloid A (SAA) levels. Ozen *et al.* (8) confirmed the higher acute phase response and suggested that rheumatic diseases were increased in the carriers. The authors concluded that this acute phase response may be reflecting a proinflammatory state in the carriers for the *MEFV* mutations. Rozenbaum *et al.* (12) have shown that their patients with FMF and juvenile idiopathic arthritis had an extremely poor prognosis suggesting that the *MEFV* mutations were affecting the severity of this inflammatory disease.

Because of the rather high incidence of ARF in our country it has been common practice to prescribe penicillin prophylaxis for patients with joint complaints. The increased history of prophylaxis for penicillin also reflects that these individuals had increased joint complaints when young. The increased complaints of fever, arthralgia, and an increase in the diagnosis of acute rheumatic fever as a child and rheumatoid arthritis in the asymptomatic parents reflect a predilection for some synovial inflammation in the surveyed

patients and confirm the above studies. In fact, ARF and rheumatic heart disease has been reported to be more frequent in the patients with FMF than in the normal population (13). Moreover, the frequency of *MEFV* mutations in the patients with rheumatic heart disease was found four times greater as compared to normal population. (14). As the genetic defect in FMF was shown to be an impaired control of inflammation, having a *MEFV* mutation might act as a susceptibility factor to certain inflammatory conditions. The site of inflammation in the carriers resembled the attack sites of the disease, namely the joint with all the aforementioned arthritis-related symptoms and the peritoneum with the abdominal pain. It may be suggested that these serosal membranes are more prone to the infiltration of phagocytes. A very recent study showed *MEFV* expression in synovial fibroblasts and the authors suggested that this might modulate other inflammatory conditions (15). Studying the apoptosis pathway at the joint and peritoneum may yield interesting results in these carriers since increased apoptosis in the peripheral blood of the FMF patients have already been demonstrated (16).

A Th1 polarization has been shown in FMF patients and carriers (17). It is known that Th1 and Th2 cells reciprocally counteract each other, it can be speculated that the prevalence of Th2-mediated disease such as allergy would be lower in patients with Th1 mediated disease. Sackesen *et al.* (18) investigated the prevalence of atopy and allergic diseases in sixty patients with FMF and their first degree relatives. They found that the prevalence of atopy and allergic rhinitis in the patients with FMF was significantly lower than in the children of the population based study. In the presented survey we also found that heterozygotes had lower prevalence of allergy to any extrinsic agent but not asthma. It may be speculated that this difference was due to the fact that asthma is multifactorial and has both Th1 and Th2 involvement. On the other hand, Brunner-Ullman *et al.* (19) found that asthma was less frequent among heterozygotes.

Not all studies have confirmed the increased inflammation in heterozygotes. When Poland *et al.* (6) studied specific glycosylation of alpha1-acid glycoprotein (AGP), an acute phase protein, they failed to show a difference in carriers of *MEFV*.

One drawback of the presented study is the high carrier rate in the Turkish population. This might have resulted in carriers within the control group as well. We have tried to overcome this with surveying a large group. Another criticism may be that some of the parents were asymptomatic patients. However, in a study of 100 healthy Turkish individuals asymptomatic compound heterozygote were detected in only 1% (4).

The presented survey is a simple but large series that shows us that indeed a number of features are more frequent in this group of obligate heterozygotes. The increased febrile episodes and joint complaints remind us that we should be careful in classifying patients as FMF when they do not have mutations in both alleles. In fact patients with atypical FMF phenotype with no mutations or one mutation only, is becoming more of a challenge. The endless discussions of the possibility of "undetectable mutations" continue. It is tempting to speculate that one *MEFV* mutation may indeed be conferring a heightened inflammation but that you may develop FMF if you have the wrong modifying genetic factors or polymorphisms.

Finally, carriers for *MEFV* mutations had an increase in inflammatory symptoms related to the serosal membranes. Thus, even one mutation in the *MEFV* gene may confer a predisposition to inflammation.

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