Influence of Some Environmental Factors on Manifestation of Familial Mediterranean Fever in Children: Clinical and Genetic Aspects

T.Avagyan[1], G.Amaryan[1,2,3], A.Budumyan[1], A.Hayrapetyan[1,4], A.Tadevosyan[1]

[1]Yerevan State Medical University after M. Heratsi
[2] "Arabkir" Medical Complex – Institute of Child and Adolescent Health
[3]National Pediatric Center for Familial Mediterranean Fever
[4]Center of Medical Genetics and Primary Health Care

Background

Familial Mediterranean Fever (FMF) is common in Armenia. Significant increase in number of cases has been registered in recent years, especially in children, including ones with atypical course. According to National Pediatric Center for Familial Mediterranean Fever (NPC FMF) during the last 13 years (from 2003 to 20016) annually diagnosed 300-350 new cases and has been recorded 6 fold increases of registered cases from 500 to more than 3000. According to Center of Medical Genetics and Primary Health Care (CMG) weekly visits for FMF diagnostics is exceeding 60, since 1997 to September 2016 there are registered more than 27000 FMF patients. Molecular-genetic testing is essential for diagnosis of FMF especially for cases with atypical course and coexistence with immune diseases as well.

It has been shown in many studies that genetic factors interacting in special way with some modifying environmental factors are able to change the character and frequency of clinical manifestation of disease (Rigante D. et al. 2006; Touitou I. et al, 2007; S. Ozen, E. Demirkaya et al, 2014).

From these aspects currently there are very intensive research on influence of modifying genes, some environmental, population factors on pathogenesis of FMF in ethnically match groups (genetic and demographic structure, climate, geography, etc.) (Livneh A., et al, 1997; Samuels J., Ozen S., 2006; S. Ozen, E. Demirkaya et al, 2014. Nevertheless, in overwhelming number of cases specific triggering factor for manifestation or the attacks of disease is not revealed.

Anyway, the dependence of phenotypic manifestations of FMF in children from certain demographic, biological, social and environmental factors (stress, diet, insolation level, etc.) was revealed in a number of studies. (Sargsyan S.1996; Amaryan G. 2010; Amaryan G. et al. 2012; Yenokyan G, Armenian HK, 2012; Karadag O, et al, 2013)

Some environmental factors, gender, serum amyloid A and number of genes, responsible for development of arthritis, Crohn's disease as well, interacting in specific way, can play a role of modifying factor in pathogenesis of FMF. In particular, the role of the environmental factor in FMF disease is also confirmed by the well-known fact of a temporary decrease in the frequency and intensity of attacks of the disease during climate change; characteristic attacks of aseptic inflammation can be triggered by stress or extreme physical exertion. Relatively often triggers of manifestation of FMF or its aggravation may become nonspecific effects like cold or prolonged exposure to cold (hypothermia), emotional stress, dietary factors, more rare – acute respiratory or intestinal infections, etc. (Karadag O, et al, 2013).

Based on above mentioned, we assessed some nonspecific enviromental factors such as cold/hypothermia, emotional stress (along with physical exhaustion), diet ("fat" food) as possible triggers of FMF manifestation in children and their interrelations with disease genotypes.

Material and methods

Medical records of 2774 children with FMF (1611 boys and 1163 girls) aged from 1 month to 18 years (mean age 7.80±0.09) have been analyzed. All patients were under follow up at National Pediatric Center for Familial Mediterranean Fever of the "Arabkir" MC-ICAH from 1997 to 2015. Diagnoses were confirmed by international criteria

Tel-Hashomer (*Livneh A. et al., 1997; Livneh A., Langevitz P., 2000)* and molecular genetic analyses of 12 most common for Armenian population mutations of MEFV *(Ajrapetyan H.., 2002).*

Only 413 (14.9% of sample) records contained information about possible triggering factors of FMF manifestation. In the rest of medical records data were either missing or patients could not mention any. Patient were questioned about cold/hypothermia, emotional stress/ physical exhaustion), diet ("fat" food) as possible triggers.

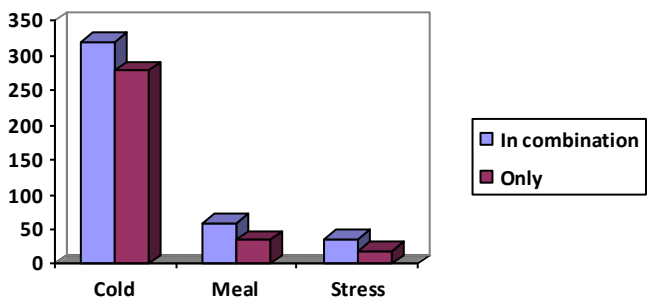
Genetic analyses were done in Center of Medical Genetics–Primary Health of Republic of Armenia on genome DNA extracted from peripheral blood of patients with FMF with special kit of regents "Puregene kit" (Gentra System, USA).

Statistical analyses were done with software SPSS 16. Categorical variables in contingency tables 2x2 were analyzed with Pearson's coefficient using Yates correction for continuity. In all cases statistical significance was considered at level $p<0.05$ (Dawson B., Trapp R., 2001).

Results and discussion

Anamnesis about some possible external factors provoking manifestation of FMF was retrieved from 413 medical records. Possible influence of most frequent mentioned factors, particularly, cold/hyperthermia, stress (emotional or prolonged physical exertion), food factor ("fat" food) on the disease onset have been analyzed (Chart 1).

Chart 1
Proposed triggers of FMF manifestation in children (numbers)



Analysis of anamnesis of children with FMF showed that the most common trigger of the manifestation of the disease was the cold factor in 319 patients out of 413 patients (77.2%). Cold factor as a separate triggering factor was mentioned in 278 (67%) children. Moreover, 41 patients along with the cold factor noticed the influence of stress and food factor as well. In the same time, as the result of MEFV testing 236 patients (74%), e.g. three quarter of diseased children were found as career of the most pathogen M694V mutation, and 56 of them (11%) had the most severe M694V homozygous genotype (M694V/M694V). Cold or hypothermia as the provoking factor of FMF onset followed by meal - "fat" food (60 patients), and less frequent - stress (36 children). One third of questioned patients were unable to point on a possible trigger of disease.

Table 1
Cold factor and genotypes of patients with FMF depending on main three *MEFV* mutations - M694V, M680I, V726A

Genotypes of MEFV	**Cold factor as the possible trigger of FMF manifestation (n= 319)**	
	Abs. Number	**%**
M694V: total	182	44.1
M694V /M694V NN..?/?M694V	56	13.6
M694V/ N	23	5.6
V726A/ other	8	1.9
V726A/ N	8	1.9
M680I/ other	2	0.5
M680I/ N	5	1.2

Thus, according to the presented data (Table 1) the most frequent triggering factor of the FMF manifestation in children was the cold / hypothermia. However, there was no significant difference in the frequency of the cold factor, depending on the type of *MEFV* mutations. It means, that, the frequency of the indications of the cold as a triggering factor for FMF onset did not depend on the type of MEFV gene mutations and this factor was equally often indicated by patients with different genotypes and mutations.

The exception was the most pathogenic M694V homozygous genotype (M694V / M694V) compared to the homozygotes for M680I mutation (M680I / M680I) (p = 0.055). In other words, the patients with M694V homozygous genotype significantly more often indicated cold as the possible trigger for FMF onset in comparison with the M680I homozygous patients.

Stress as a trigger for FMF manifestation compared with the common cold, was reported significantly less (36 patients - 8.6%). Among them 21 patients have been carriers of the M694V mutation, four patients - M680I. However, there was a statistically significant relationship between the frequency of stress indications and some MEFV genotypes (Tables 2, 3). i.e. that, the stress factor could provoke the FMF onset more often than cold. Thus, the stress as a trigger for FMF was significantly more often indicated by patients with certain MEFV mutations and genotypes, in particular, in patients with homozygous genotypes for three main MEFV gene pathogenic mutations: M694V (M694V / M694V), M680I (M680I / M680I), V726A (V726A / V726A). The carriers of M694V mutation, especially, M694V homozygotes (M694V / M694V) consisted the majority of enrolled FMF patients - 2.66 % and 0.48% respectively (Table 2). It means that stress factor significantly more frequent triggered the FMF onset than cold.

Table 2
Stress factor as the supposed trigger of FMF manifestation in children with the main three mutations M694V, M680I, V726A

Genotype MEFV	Stress factor (n = 36) as the supposed trigger of FMF manifestation	
	Abs. Number	%
M694V total	11	2.66
M694V / M694V	2	0.48
M694V/ N	4	0.97
V726A/ other	8	1.94
V726A/ N	2	0.48
M680I/ other	6	1.45
M680I/ N	1	0.24

Table 3
Stress factor and genotypes in children with FMF depending on M694V, M680I, V726A MEFV mutations

Genotypes of MEFV	Stress factor (n= 36)	
	X^2	P
M694V / M694V - M680I/other	0.172	0.288
M694V / M694V - M680I/N	3.16	0.07
M694V / M694V - M694V/other	0.093	0.129
M694V / M694V - M680I/ M680I	0.666	1
M694V /N - M680I/N	0.592	0.482
M694V /N - V726A/N	0.683	0.653
M694V /N - M694V/other	0.619	0.544
M694V / M694V - V726A/N	0.118	0.136
V726A/ V726A - V726A/N	0.751	1
V726A/ V726A - V726A/ other	0.243	0.234

According to the statistical analysis the food factor, particularly, "fat" food, did not increase the probability of the FMF manifestation.

Conclusion

Despite the fact that the cascade of inflammatory changes in FMF is partially known, triggers that provoked the onset of the disease and its attacks have not been fully studied. A number of publications indicate that factors associated with emotional or physical stress often precede attacks of the FMF and can provoke their development. It is known, that, a prolonged exposure to cold (cold / hypothermia) is also attributed to physical stress. From these positions it is supposed that stress (both emotional and physical) can be considered as the main trigger of the attacks of FMF.

The results of our study on the factors provoking the manifestation of FMF are consistent with the above data. The most frequent triggers of the onset of FMF in the sample of patients with FMF were the cold / hypothermia (67%), as well as meal (14.5%) and emotional stress (8.7%). Despite the relatively high frequency of cold indication as a trigger for the FMF manifestation, the frequency of its occurrence was widely independent of the type of MEFV mutations and genotypes, with the exception of homozygotes for the main pathogenic and the most penetrate M694V and

M680I mutations. At the same time, a statistically significant relationship was established between the emotional stress factor, which was accepted as the less frequent trigger of FMF and the three main pathogenic MEFV mutations M694V, M680I, V726A and their homozygous genotypes (M694V / M694V; M680I / M680I; V726A / V726A.

It is interesting to mention, that the common cold (as a type of physical stress) and emotional stress, as the most frequent triggers of FMF manifestation, were statistically significant more often indicated by patients with M694Vhomozygous genotype. We supposed, that on the whole, these data confirmed the role of stress - physical and emotional, as the main possible trigger for the manifestation of the FMF.

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