Triggering factors for febrile attacks in Japanese patients with familial Mediterranean fever

D. Kishida[1], A. Nakamura[1,2], M. Yazaki[3,4], K. Oka[5], A. Tsuchiya-Suzuki[1], T. Ichikawa[1], Y. Shimojima[1], Y. Sekijima[1]

[1]Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto; [2]Department of Clinical Research, National Hospital Organization Matsumoto Medical Center, Matsumoto; [3]Institute for Biomedical Sciences, Shinshu University, Matsumoto; [4]Department of Clinical Laboratory Sciences, Shinshu University School of Health Sciences, Matsumoto; [5]Department of Obstetrics and Gynaecology, Shinshu University, Matsumoto, Japan.

Dai Kishida, MD, PhD
Akinori Nakamura, MD, PhD
Masahide Yazaki, MD, PhD
Kenji Oka, MD
Ayako Tsuchiya-Suzuki, MD, PhD
Takanori Ichikawa, MD
Yasuhiro Shimojima, MD, PhD
Yoshiki Sekijima, MD, PhD

Please address correspondence to:
Dai Kishida,
Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan.
E-mail: dkishida@shinshu-u.ac.jp

Received on August 11, 2020; accepted in revised form on October 28, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 127): S76-S79.

Key words: familial Mediterranean fever, triggering factor, menstruation, MEFV mutation, colchicine

Funding: this work was supported by JSPS KAKENHI (grant numbers JP26860447 and JP17K15892).

Competing interests: none declared.

ABSTRACT

Objective. *We occasionally encounter patients with familial Mediterranean fever (FMF) whose attacks are triggered by specific factors; however, information regarding these factors is limited. Our purpose was to identify the factors that trigger febrile attacks in Japanese patients with FMF.*

Methods. *Our retrospective study included 372 patients (229 women, 143 men) with FMF, who were diagnosed between April 2007 and June 2018. We retrospectively investigated clinical features, genetic variants, and the factors that the patients perceived to have triggered their attacks. Patients completed a questionnaire that included the following triggering factors, anxiety, psychological stress, tiredness, excitement, environmental change, and menstruation.*

Results. *Of 372 patients, 180 (49.4%) reported some triggering factors. Psychological stress and tiredness were commonly reported factors regardless of sex; however, menstruation (39.7%, n=91) was the most commonly reported triggering factor in female patients with FMF. Menstrual-related patients had a younger age of onset and diagnosis, a higher frequency of peritonitis, and a higher rate of patients with endometriosis compared with the non-menstrual-related patients.*

Conclusion. *Gaining an understanding of these triggering factors could help to reduce attacks and educate the patients. Clinicians may need to consider FMF for patients who have fever and serositis that occurs with every menstrual period.*

Introduction

Familial Mediterranean fever (FMF) is a typical auto-inflammatory disease characterised by recurrent episodes of fever and polyserositis. Patients are widespread not only in the Mediterranean region but also in Europe and Japan. Clinical manifestations are thought to differ slightly between populations due to differences in genetic and environmental factors (1). However, febrile attacks of FMF occur unexpectedly regardless of ethnicity, and frequent attacks can impair a patient's daily life.

The pathomechanism of the febrile attacks is not fully understood. FMF is associated with mutations in the *MEFV* gene, which encodes the pyrin protein. Recent studies have demonstrated that pyrin dephosphorylation causes the activation of pyrin inflammasome and the subsequent release of proinflammatory cytokines such as interleukin (IL)-1β and IL-18 (2, 3). Furthermore, patients with homozygous mutations have been reported to be associated with severe disease phenotype (4). On the other hand, patients often report that attacks can be triggered by a variety of factors. Physical and emotional stress, exposure to cold, menstruation, and other factors are known as triggers; however, the details remain unknown (5). There are few reports on the association of triggering factors with clinical symptoms or *MEFV* variants (6, 7), and to date, there has been no consensus. Thus, understanding these factors can be useful to prevent attacks and educate the patients.

In this study, we aimed to identify the triggering factors for the attack in Japanese patients with FMF, and to examine the association between each triggering factor and clinical and genetic characteristics.

Materials and methods

Between April 2007 and June 2018, 372 patients who were clinically diagnosed with FMF, and referred to Shinshu University (Department of Medicine [Neurology and Rheumatology]) for *MEFV*

genetic analysis from medical institutions throughout Japan were included in this retrospective study. All patients fulfilled the diagnostic criteria for FMF [Livneh criteria (8)]. Patients whose clinical course after genetic analysis was unknown or who were eventually diagnosed with other diseases were excluded regardless of the existence of the genetic mutation. We retrospectively investigated clinical features including comorbidities and genetic variants of these patients. In addition, we examined the patients' perception of the factors that trigger recurrent febrile attacks. Patients were shown a list that included the following factors: anxiety, psychological stress, tiredness, excitement, environmental change, menstruation, and other factors (patients were free to list other factors), and asked whether these factors trigger febrile attacks. From March 2016 onwards, the presence of endometriosis was also investigated by questioning from the attending physician to examine its association with menstruation. To unify the survey method, patients were evaluated by each attending physician using the same survey sheet regarding clinical information. Each triggering factor was analysed by sex, and the relationship with clinical and genetic features was examined. The analysis of the *MEFV* gene variants was performed by direct sequencing of the polymerase chain reaction amplification products for hotspot regions (exons 1, 2, 3, 5, and 10), as described previously (9).

Informed consent for the *MEFV* genetic screening and for the publication of their clinical characteristics anonymously was obtained from all patients prior to their participation in the genetic study. The *MEFV* genetic study was approved by the Institutional Review Board (no. 314 and 572) of the Shinshu University School of Medicine.

Statistical analysis

Differences among categorical variables were analysed using the chi-square test. Continuous variables were evaluated using Welch's *t* test. In all analyses, $p<0.05$ was considered statistically significant. Values are expressed as the mean ± standard deviation.

Table I. Characteristics of the patients with familial Mediterranean fever included in the study.

	n=372
Demographic features	
Men / Women	143 / 229
Age at onset, years (mean ± SD)	26.5 ± 16.1
Age at diagnosis, years (mean ± SD)	36.8 ± 16.3
Positive family history	61 (16.4%)
Positive triggering factor	180 (49.4%)
Clinical symptoms	
Frequency of attacks, per year (mean ± SD)	12.5 ± 11.9
Fever	353 (94.9%)
Peritonitis	232 (62.4%)
Pleuritis	154 (41.4%)
Arthritis	160 (43.0%)
Headache	133 (34.9%)
Myalgia	82 (22.0%)
Erysipelas-like erythema	16 (4.3%)
Treatment	
Administration of colchicine	302 (81.2%)
Good response to colchicine	279 (92.4%)

Results

A total of 372 patients (229 women, 143 men) were included in this study. The demographic and clinical characteristics of the patients are shown in Table I. The mean age of disease onset was 26.5±16.1 years, and it took approximately 10 years for the patients to be diagnosed with FMF. The frequency of attacks was 12.5±11.9 times per year. The ratio of good response to colchicine treatment (asymptomatic or occasional attacks) was 92.4%.

One hundred and eighty patients (49.4%) reported some triggering factors. Each triggering factor by sex is shown in Table II. Although psychological stress and tiredness were common triggering factors regardless of sex, menstruation was the most common factor that triggered febrile attack in female patients. There was no significant difference between men and women without menstruation. Other factors included exposure to sunshine (n=2), excitement (n=2), and consuming alcohol, heat, and constipation (n=1, each).

The clinical and genetic characteristics of the female patients whose attacks were triggered by menstruation (menstrual-related (MR) patients) are shown in Table III. The age at onset and the age at diagnosis in these patients was 21.7±9.6 years and 32.1±9.4 years, respectively. The MR patients were significantly younger compared with the non-MR patients. Moreover, 74.7% of the patients in the MR group had peritonitis at the time of the attacks, which was significantly higher than that in the non-MR group. The frequency of attacks, the percentage of symptoms other than peritonitis, and the response to colchicine treatment were not significantly different between the two groups. Meanwhile, the proportion of patients with endometriosis was significantly higher in the MR group (36.6% *vs*. 7.7%). Genetically, the frequency of the p.M694I mutation was higher in MR patients, but this was not statistically significant.

Discussion

This study investigated the factors that the patients had perceived to have triggered their FMF attacks. This is the first study to examine the triggering factors for an FMF attack in Japanese patients. Our results revealed that approximately half of the patients with FMF reported some triggering factors, and that menstruation was the most common triggering factor in female patients. Furthermore, MR patients had a younger age of onset, a higher frequency of peritonitis, and a higher rate

Table II. Triggering factors prior to the attacks.

Factor	Men (n=143)	Women (n=229)
Menstruation	-	91 (39.7%)
Psychological stress	47 (32.9%)	76 (33.2%)
Tiredness	47 (32.9%)	73 (31.9%)
Environmental change	7 (4.9%)	8 (3.5%)
Anxiety	4 (2.8%)	13 (5.7%)
Overeating	3 (2.1%)	2 (0.9%)
Cold exposure	1 (0.7%)	3 (1.3%)
Vigorous exercise	1 (0.7%)	2 (0.9%)
Other factors	3 (2.1%)	4 (1.7%)

Table III. The characteristics of the female patients whose attacks of familial Mediterranean fever are triggered by menstruation.

	Menstrual-related group (n=91)	Non-menstrual-related group (n=138)	*p*
Clinical features			
Age at onset	21.7 ± 9.6	27.2 ± 17.2	0.002
Age at diagnosis	32.1 ± 9.4	37.1 ± 17.8	0.006
Frequency of attacks	11.2 ± 7.3	12.1 ± 11.6	0.44
Fever	87 (95.6%)	131 (95.0%)	0.67
Peritonitis	68 (74.7%)	75 (54.3%)	0.001
Pleuritis	36 (39.6%)	57 (41.3%)	0.79
Arthritis	45 (49.5%)	67 (48.6%)	0.89
Headache	37 (40.7%)	57 (41.3%)	0.92
Administration of colchicine	73 (80.2%)	111 (80.4%)	0.79
Good response to colchicine	66 (90.4%)	105 (94.6%)	0.26
Having endometriosis*	15 (36.6%)	4 (7.7%)	<0.001
Genetic features			
p.M694I	25 (27.5%)	24 (17.4%)	0.068
p.E148Q	46 (50.5%)	82 (59.4%)	0.18
p.L110P	13 (14.3%)	26 (18.8%)	0.36
p.R202Q	7 (7.7%)	10 (7.2%)	0.89
p.G304R	4 (4.4%)	6 (4.3%)	0.98
p.P369S	11 (12.1%)	12 (8.7%)	0.40
p.R408Q	9 (9.9%)	9 (6.5%)	0.35
p.S503C	3 (3.3%)	3 (2.2%)	0.60
p.E84K	1 (1.1%)	8 (5.8%)	0.073

*n=93 (41 in the menstrual-related group and 52 in the non-menstrual group).

of endometriosis compared with non-MR patients.

There have been few studies that have compared multiple triggering factors. Karadag *et al*. have reported that cold exposure, emotional stress, tiredness, and menstruation are associated with serositis, and long-lasting standing, long-duration travel, and tiredness are associated with musculoskeletal symptoms (6). Yenokyan *et al*. have found that multiple stressful events can predict FMF attacks (7). Our study also found that psychological stress was one of the major triggering factors; however, when limited to female patients, menstruation was a more common triggering factor.

Several studies have reported a relationship between FMF attacks and menstruation. However, the frequency of patients whose attacks were associated with menstruation varies widely from 7% to 79% (10-12). These differences may be ascribed to differences in survey methods. Ben-Chetrit *et al*. (10) have described that attacks are associated with menstruation in 7% of the patients, but they included patients whose attacks are preceded only by menstruation. On the other hand, Guzelant *et al*. (12) have reported that 79% of the patients have FMF attacks with menstruation, but they have evaluated whether patients experience flares around the menstrual period. It may be better to consider these differences when we discuss the association between FMF attacks and menstruation. In our study, we requested that the patients list the factors that they perceived to be triggers, and 39.7% of the female patients cited menstruation.

Although the precise mechanisms by which menstruation affects FMF attacks are unknown, there are several possible theories. One theory is that there is a decrease in sex hormones during the menstrual phase. Oestrogen inhibits tubulin assembly and adhesion molecule expression, and thus may have similar effects to colchicine, and inhibit the activation of pyrin inflammasome (10). On the other hand, the relationship between progesterone and FMF is unclear, but etiological studies have reported that progesterone controls the production of prostaglandins (13). Recently, a case series of patients with FMF who were diagnosed with menstrual fever and successfully treated using colchicine and dienogest (a progesterone receptor agonist) was reported (14). Dienogest has been reported to inhibit Toll-like receptor (TLR) 4, signalling by direct suppression of nuclear factor-κB in human endometrial epithelial cells (15). Based on these findings, both oestrogen and progesterone may contribute to the pathomechanism of the disease. Another theory is the direct influence of menstruation itself. It has been found that a variety of stimuli, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate inflammasome (16). During menstruation, breakdown of the endometrial tissue may elicit a stressful reaction in the tissues (17). These stimuli may act as DAMPs, making them more likely to trigger attacks in female patients with FMF. The expression levels of proinflammatory cytokine genes, including IL-1β, are significantly increased in the menstrual phase in primary dysmenorrhea (18).

In this study, we demonstrated that the proportion of MR patients with endometriosis was significantly higher compared with non-MR patients (36.6% *vs*. 7.7%). This finding is clearly higher than the prevalence of endometriosis in the general population (approximately 10%). Initially, it was thought that these patients might have dysmenorrhea rather than FMF. Actually, a high frequency of misdiagnosis has been reported even in a cohort of patients registered after year 2000 (19). However, we could distinguish FMF from dysmenorrhea based on: whether patients had a high fever and an elevated acute inflammatory response at each episode, the presence of pleuritis and arthritis in many patients, and a good response to colchicine treatment. The reason for the high prevalence of endometriosis in the MR group is unclear; however, the involvement of the innate immune system in the pathogenesis of endometriosis has been reported. The infiltration of macrophages into the endometrium is increased in women with endometriosis (20), and the expression levels of TRL4 from the endometriosis lesions are higher than those from the

eutopic endometrium (21). The attacks can be triggered by menstruation in female FMF patients; however, attacks may be more likely to be induced for patients with endometriosis.

The quality of life for patients with FMF is impaired compared with that of healthy subjects (22, 23). Indeed, unexpected febrile attacks force patients to alter or abandon their plans. This study showed that approximately half of the patients with FMF reported some triggering factors. Understanding these factors may be useful for attack reduction and patient education. We think that it is important to examine whether patients with FMF had some triggering factors for recurrent febrile attacks.

This study has several limitations. Responses to triggering factors were self-reported and depended on the patient's ability to recall past events. Also, the list of triggering factors that we used for the survey did not include "cold exposure". The factor "cold exposure" is reported to be the most common factor for serositis in a retrospective study from Turkey conducted in 2013 (6). However, our survey began in 2007, and only about 1% of the patients listed cold exposure, although we allowed them to freely include factors that were not on the list. Clinical manifestations are reported to be different slightly between populations (1), thus these findings may be due to ethnic differences. Another limitation is that not all of the patients in the non-MR group were able to confirm that they were not pre-menarche or post-menopausal. Additionally, the presence of endometriosis was not examined in all patients. A larger investigation may reveal further information about the relationship between endometriosis and FMF.

In conclusion, approximately half of the Japanese patients with FMF were aware that specific factors could trigger their attacks. It is important to gain an understanding of these factors to provide guidance for the patients. Menstruation was the most commonly reported triggering factor in female patients, and MR patients had endometriosis more frequently than the non-MR patients. We may need to suspect FMF when we encounter patients with fever and serositis that occur with every menstrual period.

Acknowledgments

The authors thank all the doctors for participating in the current study. The authors thank Ms Sonomi Nagasaki and Ms Emi Nomura for their technical support.

References

1. BEN-CHETRIT E, YAZICI H: Familial Mediterranean fever: different faces around the world. *Clin Exp Rheumatol* 2019; 37 (Suppl. 121): S18-22.
2. MAGNOTTI F, LEFEUVRE L, BENEZECH S *et al*.: Pyrin dephosphorylation is sufficient to trigger inflammasome activation in familial Mediterranean fever patients. *EMBO Mol Med* 2019; 11: e10547.
3. JAMILLOUX Y, MAGNOTTI F, BELOT A, HENRY T: The pyrin inflammasome: from sensing RhoA GTPases-inhibiting toxins to triggering autoinflammatory syndromes. *Pathog Dis* 2018; 76.
4. AKTAŞ A, KARADAVUT M, CANSU D, KORKMAZ C: The influence of genotype on disease severity and concomitant diseases in familial Mediterranean fever patients. *Clin Exp Rheumatol* 2019; 37 (Suppl. 121): S93-7.
5. FONNESU C, CERQUAGLIA C, GIOVINALE M *et al*.: Familial Mediterranean Fever: a review for clinical management. *Joint Bone Spine* 2009; 76: 227-33.
6. KARADAG O, TUFAN A, YAZISIZ V *et al*.: The factors considered as trigger for the attacks in patients with familial Mediterranean fever. *Rheumatol Int* 2013; 33: 893-7.
7. YENOKYAN G, ARMENIAN HK: Triggers for attacks in familial Mediterranean fever: application of the case-crossover design. *Am J Epidemiol* 2012; 175: 1054-61.
8. LIVNEH A, LANGEVITZ P, ZEMER D *et al*.: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40: 1879-85.
9. KISHIDA D, NAKAMURA A, YAZAKI M, TSUCHIYA-SUZUKI A, MATSUDA M, IKEDA S: Genotype-phenotype correlation in Japanese patients with familial Mediterranean fever: differences in genotype and clinical features between Japanese and Mediterranean populations. *Arthritis Res Ther* 2014; 16: 439.
10. BEN-CHETRIT E, BEN-CHETRIT A: Familial Mediterranean fever and menstruation. *BJOG* 2001; 108: 403-7.
11. AKAR S, SOYTURK M, ONEN F, TUNCA M: The relations between attacks and menstrual periods and pregnancies of familial Mediterranean fever patients. *Rheumatol Int* 2006; 26: 676-9.
12. GUZELANT G, OZGULER Y, ESATOGLU SN *et al*.: Exacerbation of Behçet's syndrome and familial Mediterranean fever with menstruation. *Clin Exp Rheumatol* 2017; 35 (Suppl. 108): S95-9.
13. IACOVIDES S, AVIDON I, BAKER FC: What we know about primary dysmenorrhea today: a critical review. *Hum Reprod Update* 2015; 21: 762-78.
14. OKA K, HIGUCHI S, KISHIDA D *et al*.: Eight cases of Familial Mediterranean fever diagnosed by menstrual fever. *The Journal of Japan Society for Menopause and Women's Health* 2017; 25: 34-38 [Article in Japanese].
15. MITA S, SHIMIZU Y, NOTSU T, IMADA K, KYO S: Dienogest inhibits Toll-like receptor 4 expression induced by costimulation of lipopolysaccharide and high-mobility group box 1 in endometrial epithelial cells. *Fertil Steril* 2011; 96: 1485-9.e4.
16. MALIK A, KANNEGANTI TD: Inflammasome activation and assembly at a glance. *J Cell Sci* 2017; 130: 3955-63.
17. IMAMURA T, KHAN KN, FUJISHITA A *et al*.: Effect of GnRH agonist therapy on the expression of human heat shock protein 70 in eutopic and ectopic endometria of women with endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2014; 180: 16-23.
18. MA H, HONG M, DUAN J *et al*.: Altered cytokine gene expression in peripheral blood monocytes across the menstrual cycle in primary dysmenorrhea: a case-control study. *PloS One* 2013; 8: e55200.
19. ERDOGAN M, UGURLU S, OZDOGAN H, SEYAHI E: Familial Mediterranean fever: misdiagnosis and diagnostic delay in Turkey. *Clin Exp Rheumatol* 2019; 37 (Suppl. 121): S119-24.
20. KHAN KN, MASUZAKI H, FUJISHITA A, KITAJIMA M, SEKINE I, ISHIMARU T: Differential macrophage infiltration in early and advanced endometriosis and adjacent peritoneum. *Fertil Steril* 2004; 81: 652-61.
21. HAYASHI C, CHISHIMA F, SUGITANI M *et al*.: Relationship between Toll-like receptor-4 and mPGES-1 gene expression in local lesions of endometriosis patients. *Am J Reprod Immunol* 2013; 69: 231-9.
22. BUSKILA D, ZAKS N, NEUMANN L *et al*.: Quality of life of patients with familial Mediterranean fever. *Clin Exp Rheumatol* 1997; 15: 355-60.
23. SAHIN S, YALCIN I, SENEL S *et al*.: Assesment life quality of familial Mediterranean fever patients by short form-36 and its relationship with disease parameters. *Eur Rev Med Pharmacol Sci* 2013; 17: 958-63.