

[CASE REPORT]

Cold Exposure Related Fever with an Mediterranean Fever (MEFV) Gene Mutation

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Abstract:

Familial Mediterranean fever (FMF) is a genetic autoinflammatory disease characterized by recurrent fever with serosal inflammation. We experienced a 53-year-old male who had been suffering from periodic attacks with slight fever and myalgia which were mainly triggered by cold exposure in winter. Although his clinical course did not satisfy the criteria for familial Mediterranean fever, heterozygous E148Q/M694I mutation in the Mediterranean fever (MEFV) gene was detected. Further attacks were prevented by treatment with colchicine. Attention should therefore be paid to the possibility of atypical FMF symptoms, which should be accurately diagnosed by genetic analyses to prevent the development of amyloidosis.

Key words: FMF, MEFV, periodic fever, E148Q/M694I

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Introduction

Familial Mediterranean fever (FMF) is a genetic autoinflammatory disease characterized by recurrent fever with serosal inflammation and it is a relatively common disease among Sephardic Jews, Arabs, Turks, and Armenians. FMF is considered to be rare in Japan (1), and the clinical features in Japanese tend to be milder than those observed in the Mediterranean population due to different genotypes of the Mediterranean fever (MEFV) gene, which is considered to be the responsible gene for FMF, in Japanese patients and Mediterranean patients (2). AA amyloidosis is the most serious complication of FMF. The prevalence of AA amyloidosis is low in Japanese FMF patients in comparison to that observed in Mediterranean patients (3) because few Japanese patients have the M694V mutation, which is the most popular mutation in the Mediterranean population and it is regarded as a significant risk factor of AA amyloidosis. Colchicine suppresses attacks, resulting in the prevention of AA amyloidosis (4). More than 90% of Japanese FMF patients respond to treatment with colchicine. Therefore, making a correct diagnosis of FMF, especially in patients with atypical symptoms, is important. We herein show an atypical

clinical course of FMF in a middle-aged patient who had been suffering from cold temperature-related attacks.

Case Report

In March 2016, a 53-year-old Japanese male who lived in Hokkaido was referred to our institution due to recurrent attacks of slight fever and myalgia with prominent inflammatory reaction shown by laboratory investigation every winter during the past 4 years. He experienced the attacks once or twice every month mainly during winter, especially after hard physical labor or standing outside for a long time (Fig. 1). Each episode of fever lasted for only 1 day. However, he had never experienced any attacks in summer, even after hard physical labor such as agricultural work. Although blood tests had been performed several times, no definitive diagnosis had been made.

On his first visit to our institution, 2 days after his most recent attack, his body temperature had returned to normal, but the laboratory data revealed a mild inflammatory condition (Table). No bacteria were detected in his urine sediment. Computed tomography of the head, chest, abdomen, and pelvis showed no obvious explanation for his recurrent attacks. He had no familial history of connective tissue dis-

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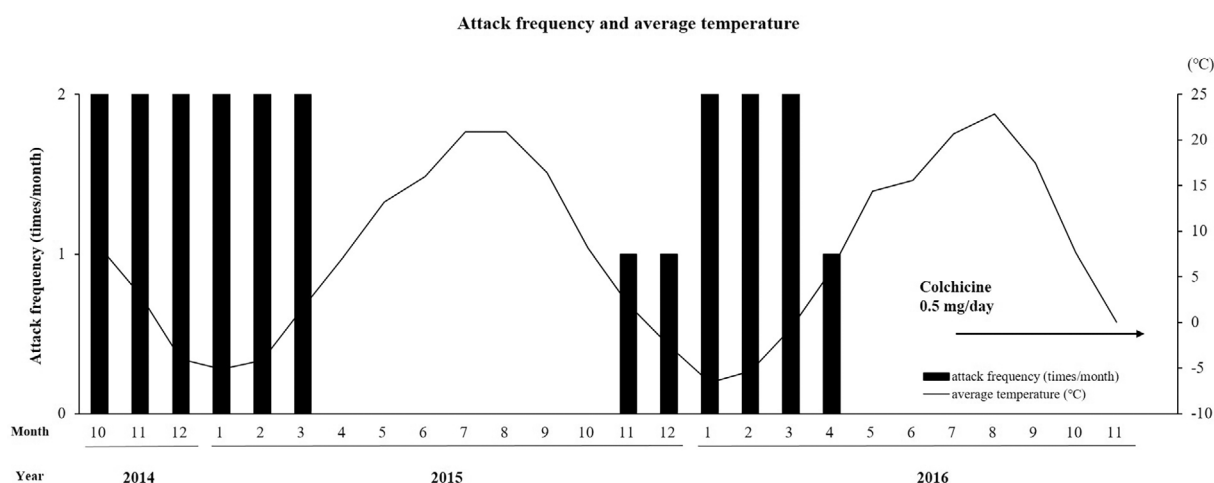


Figure 1. This figure shows the relation between attacks and temperature in the past 2 years. Cold exposure was thought to be the main factor triggering the attacks. Average temperature was obtained from the web page of the Japan Meteorological Agency on November 23, 2016. www.jma.go.jp/jma/index.html

Table. Laboratory Findings.

Peripheral blood counts		Biochemistry					
WBC	6,290/ μ L	TP	7.1g/dL	Na	141mmol/L	ANA	< \times 40
Neu	65.30%	Alb	4.2g/dL	K	4.3mmol/L	RF	(-)
Ly	26.90%	BUN	10.5mg/dL	Cl	106mmol/L	Anti-CCP Ab	(-)
Mono	6.00%	Cre	0.73mg/dL	CRP	3.68mg/dL		
Eosino	0.80%	T-bil	0.5mg/dL	PCT	0.05ng/mL	P-ANCA	(-)
Baso	1.00%	AST	22U/L	MMP3	62.8ng/mL	C-ANCA	(-)
RBC	484 \times 10 ⁴ / μ L	ALT	21U/L	sIL-2R	234U/mL		
Hb	15.1g/dL	LDH	168U/L				
Plt	22.1 \times 10 ⁴ / μ L	ALP	252U/L				
ESR	15mm/h	AMY	63U/L				
		CK	116U/L				
		Tchol	189mg/dL				
		TG	103mg/dL				

WBC: white blood cell count, Neu: neutrophil, Ly: lymphocyte, Mono: monocyte, Eosino: eosinophil, Baso: basophil, RBC: red blood cell count, Hb: hemoglobin, Plt: platelets, ESR: erythrocyte sedimentation rate, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, AMY: amylase, CK: creatine kinase, Tchol: total cholesterol, TG: triglyceride, CRP: C-reactive Protein, PCT: procalcitonin, MMP3: matrix metalloproteinase 3, sIL-2R: soluble interleukin-2 receptor, ANA: anti-nuclear antibody, RF: rheumatoid factor, Anti-CCP Ab: Anti-cyclic citrullinated peptide antibody, P-ANCA: perinuclear anti-neutrophil cytoplasmic antibody, C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody

ease or autoinflammatory disease. We found an extremely high level of serum amyloid A (SAA) one day after another attack (WBC: 9,220/ μ L: C-reactive protein (CRP): 10.67 mg/dL, SAA: 1,430 μ g/mL). However, during the interval between attacks, he was symptom-free and the laboratory data of inflammatory reaction decreased to normal levels.

His clinical course did not satisfy the criteria for familial Mediterranean fever (5). However, it is known that some FMF patients show atypical symptoms including slight fever, myalgia, and arthralgia. Therefore, all exons of the MEFV gene in the patient were sequenced, and heterozy-

gous E148Q in exon 2 and M694I in exon 10 were thus identified (Fig. 2). Although 5 months have passed since the start of colchicine administration at 0.5 mg/day and it is winter now, the patient has been free of any attacks.

Discussion

Autoinflammatory diseases are defined as illnesses caused by inappropriate inflammation due to innate immune system dysfunction with a hyperproduction of interleukin (IL)-1 β . FMF is one of the most common autoinflammatory diseases

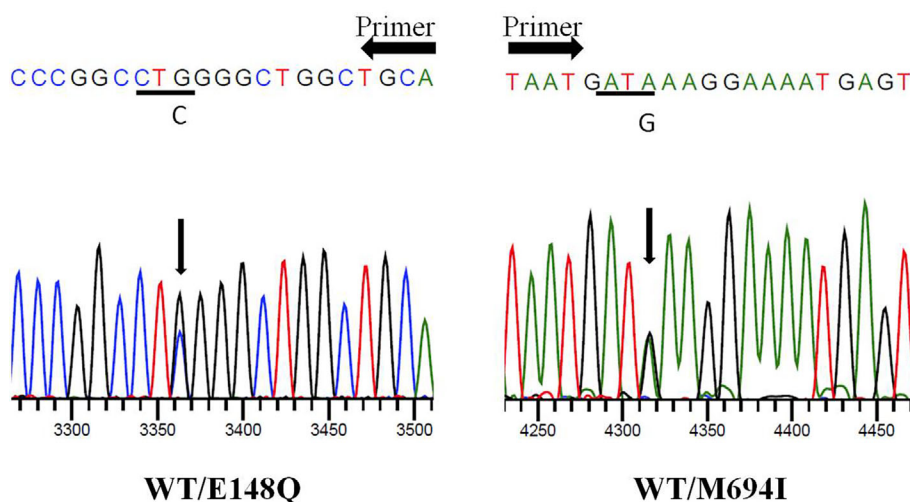


Figure 2. Analysis of the MEFV gene of the patient. The C to G transition in codon 148 and the G to A transition in codon 694 converted E to Q and M to I, respectively.

with a genetic disorder and it is clinically characterized by recurrent fever with serosal inflammation. The attacks are thought to be caused by the gain of function of pyrin, which is encoded by the MEFV gene (6). Renal amyloidosis is the most serious complication of FMF. Treatment with colchicine can drastically reduce the incidence of attacks of FMF, thus leading to the prevention of the development of amyloidosis. Therefore, an accurate diagnosis for repeated attacks is very important in clinical practice.

In Japan, E148Q/M694I mutation in the MEFV gene is the most popular mutation in FMF patients, having been found in 20.4% of Japanese FMF patients (7). M694I mutation has been reported to be rarely observed among healthy subjects in Japan, while the E148Q mutation has been frequently found (7). The methionine residue in codon 694 plays a crucial role in the pyrin function (8). Therefore, mutations in this codon tend to be associated with a severe phenotype of FMF such as early onset and high frequency of attacks. Recently, mutations in inflammasome-related genes including polymorphisms of Toll-like receptor 2, SAA, or IL-1b gene have been suggested to be involved in the FMF phenotype (9), which would partly explain why patients possessing the same mutation show different phenotypes. Clinically, some factors including standing for a long period, tiredness, and cold exposure are known to be triggers of an FMF attack (10). Cold exposure was thought to be the main factor triggering attacks in our patient. However, it is not clear precisely how cold exposure evokes inflammation in FMF patients. Interestingly, cold exposure is known to be a cause of attacks in some other autoinflammatory diseases, such as familial cold-induced autoinflammatory syndrome (FACS) and nucleotide-binding domain and leucine-rich repeat-containing protein (NLRP) 12-associated periodic syndrome (11). A previous study showed that monocytes from FACS patients and bone marrow-derived dendritic cells from transgenic mice with NLRP3 mutation, a genetic mutation responsible for FACS, induced IL-1b re-

lease by 32°C incubation *in vitro* (12). It was also shown in that study that the stability of mutated NLRP3 increased at a lower temperature, suggesting that the accumulation of an abnormal protein induces attacks under conditions of cold exposure by gain of function. In the same way, a cold temperature might evoke attacks in FMF patients by affecting the stability of abnormal pyrin, which should be degraded.

According to a previous report, patients carrying the E148Q/M694I mutation tend to show a severe phenotype of FMF with early onset and high-grade fever (2). The average age at onset of FMF with E148Q/M694I mutation is 18.8 years, ranging from 9 years to 34 years. In our patient, the first attack was observed at 49 years of age, showing a low grade fever. Although the cause of a mild phenotype of this disease is unclear, an epigenetic modification or mutation of the promoter region of pyrin might delay the onset of FMF and prevent the onset of a high-grade fever since the phenotype depends on the amount of protein that gains an abnormal function.

As far as we know, this is the first report of cold exposure-related fever and myalgia caused by a mutation of the MEFV gene in Japan. FMF is not a familiar disease for general physicians in Japan, and the diagnosis of FMF usually takes more than 20 years from the first attack. Since the clinical course of this case would usually be regarded as a refractory transient viral infection in a clinical setting, attention should be paid to the possibility of MEFV gene mutation with atypical FMF symptoms, which should be accurately diagnosed by genetic analyses.

The authors state that they have no Conflict of Interest (COI).

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