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【 CASE REPORT 】

Five Cases of Familial Mediterranean Fever in Japan: The Relationship with *MEFV* Mutations

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Abstract:

Familial Mediterranean fever (FMF) is the most common genetic autoinflammatory disease, but it has been considered a rare disease in Japan. We herein describe five patients with FMF who were diagnosed both clinically and genetically at a single Japanese institute. A genetic investigation of *Mediterranean fever* (*MEFV*) detected heterozygosity for the compound mutations L110P/E148Q (n=2) and L110P/148Q/P369S/R 406Q (n=1), and heterozygosity for M694I (n=1) and S503C (n=1). Colchicine prevented febrile attacks and accompanying symptoms in four patients. One patient with an S503C mutation showed resistance. Physicians should be aware of the characteristic symptoms, as well as the more unusual symptoms such as headache, when diagnosing FMF.

Key words: aseptic meningitis, familial Mediterranean fever, headache, Japan, periodic fever, inflammatory disease

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Introduction

Familial Mediterranean fever (FMF) is the most common genetic autoinflammatory disease (1). FMF predominantly affects populations from the Mediterranean (2), but our nationwide survey identified a larger than expected number of such patients in Japan (3). The underlying cause of FMF is a mutation in *Mediterranean fever* (*MEFV*) (4). Genotype-phenotype correlations studied in Japan suggest that mutations within *MEFV* exon 10 are associated with a typical FMF phenotype, whereas mutations within exons 2 or 3 are associated with an incomplete FMF phenotype (5).

We herein describe our experience with five Japanese patients with FMF, who were diagnosed using clinical and genetic analyses in a single department of general internal medicine at a university hospital. All cases were diagnosed according to the Tel-Hashomer criteria (Livneh revision, 1997) (6). One patient with an *MEFV* exon 10 mutation presented with a typical FMF phenotype including periodic fever and abdominal pain. The remaining four patients with an incomplete FMF phenotype presented with uncommon FMF manifestations including headache. We discuss the importance of genotype-phenotype correlations in Japanese patients with FMF.

MEFV analysis

Genomic DNA was extracted from whole blood using the Promega Wizard® Genomic DNA Purification Kit (Madison, USA) according to the manufacturer's instructions. Polym-

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erase chain reaction (PCR) was performed using forward and reverse primers for each *MEFV* exon, as described previously (5). Written informed consent for this case report and to perform genetic analyses was obtained from all patients.

Case Reports

Case 1

A 53-year-old Japanese male patient with periodic fever and bilateral ankle joint arthritis was referred to our department. He had experienced periodic fever attacks lasting 3 days, and had suffered bilateral ankle joint tenderness and swelling since his 20s. At the age of 51, he began to experience frequent febrile attacks (occurring within 3 days of fever, approximately every 3 weeks, with temperatures of around 38℃) with abdominal and anal pain and polyarthralgia. The bilateral knee and hip joints were also involved.

His physical examination was normal. His complete blood counts, liver function test, and urinalysis (no proteinuria) were also normal, but his serum creatinine level (Cr; 1.34 mg/dL) was slightly elevated. Use of a colon fiberscope found no abnormalities, including amyloid deposits, so a renal biopsy was not performed. An *MEFV* analysis detected a heterozygote M694I mutation in exon 10.

His abdominal pain was diagnosed as peritonitis, and his febrile attacks were consistent with typical FMF; they disappeared after colchicine treatment (1.0 mg/day).

Case 2

A 48-year-old Japanese female patient was taken to our hospital by ambulance with convulsions followed by a decreased level of consciousness. Since the age of 45, she had experienced periodic fever lasting 3 days with back pain, severe occipital headache with no signs of meningitis, and arthritis of the elbow and knee joints every month.

On admission, she was unconscious and had neck stiffness that indicated the possibility of meningitis. Brain magnetic resonance imaging (MRI) and an electroencephalogram showed no abnormal findings. A cerebrospinal fluid analysis revealed an opening pressure of 24 cm H_2O, an elevated protein concentration (154 mg/dL), but cellularity (12/mm^3) and glucose (79 mg/dL, serum glucose 167 mg/dL) within normal ranges. No microbes were detected by Gram staining, acid-fast staining, ink staining, cultivation, or PCR for acid-fast bacilli and *Mycobacterium* tuberculosis. Viral antigen tests for herpes simples virus (HSV)-1, HSV-2, and varicella zoster virus (VZV) were also negative. These findings were consistent with aseptic meningitis. She was referred to our department from the Department of Neurology for further examination for periodic fever.

Laboratory tests were normal except for an elevated white blood cell count (WBC; 12,530/μL) and C-reactive protein (CRP; 9.32 mg/dL). An *MEFV* analysis showed a compound heterozygous mutation (L110P/E148Q) in exon 2. She was diagnosed with an incomplete type of FMF and was treated with colchicine (0.5 mg/day), which eradicated her febrile attacks and headache.

Case 3

A 40-year-old male had periodic fever, polyarthralgia, headache, and abdominal and back pain. He had suffered a recurrent high fever (>38℃) since he was 28 years old. His periodic fever lasted for 4 to 7 days and occurred at a frequency of once every 2 to 3 months. Each febrile attack caused a headache in the occipital region together with posterior cervical spine pain, but there were no signs of meningitis. His bilateral wrist and ankle joints showed severe inflammatory changes, such as pain on exercise, swelling, and warmth. Slight swelling of the elbow joints was also recognized.

His physical examination was unremarkable. Laboratory tests were normal, except for an elevated WBC (10,930/μL), CRP (1.27 mg/dL), and serum amyloid A (SAA; 189.7 μg/mL). An *MEFV* analysis revealed a heterozygous mutation in exon 2 (L110P/E148Q). Both abdominal and back pain were diagnosed as peritonitis and pleuritis, respectively. He was diagnosed with an incomplete type of FMF. He was treated with colchicine (1.0 mg/day), which led to the disappearance of the febrile attacks.

Case 4

A 25-year-old male presented with high fever with bilateral pleuritic chest pain, respiratory distress, polyarthralgia, and occipital headache. His febrile attacks occurred every 2 weeks and involved a fever of 38.0 to 38.5℃ which lasted 3 days. The febrile attacks were always accompanied by headache with no meningeal signs. Physical examination was unremarkable except for swelling of the bilateral knee, hip, and ankle joints.

Laboratory tests revealed the presence of high acute phase reactants (CRP, 10.64 mg/dL; SAA, 844.4 μg/mL) and leukocytosis (WBC, 30,400/μL) during the febrile attacks. Other laboratory data were normal. An *MEFV* analysis revealed heterozygous mutations in exon 2 (L110P/E148Q) and exon 3 (P369S/R408Q).

Chest symptoms were diagnosed as pleuritis. He was diagnosed with an incomplete type of FMF and was treated with colchicine (0.5 mg/day), which promptly reduced the febrile attacks. Complete elimination of the attacks was achieved by increasing the colchicine dose to 1.5 mg/day.

Case 5

A 47-year-old male was referred to our department with a fever of no apparent cause. He had recognized periodic fever (>40℃) lasting for 3 days every 2 months since the age of 25. At the age of 42, the frequency of the periodic fever increased (to an interval of almost every 10 days), and was accompanied by occipital headache, nausea, diarrhea, abdominal pain, and polyarthralgia. Arthralgia was detected in the bilateral knee, hip, and elbow joints. Nausea also oc-

Table 1. Demographic and Clinical Features of the Five FMF Patients.

Patient	Sex	Age (yr)	Onset (yr)	Delay (yr)	Febrile attack		Accompany symptoms of FMF			MEFV mutation	Pretreatment			Posttreatment			Colchicine (mg/day)	Treatment resistance
					Fre (mo)	Dur (day)	Serositis	Arthritis	Headache		WBC (/μL)	CRP (mg/dL)	SAA (μg/dL)	WBC (/μL)	CRP (mg/dL)	SAA (μg/dL)		
1	M	53	20	33	<1	3	Peritonitis	poly	-	exon10 (M694I/-)	7,270	5.72	N.A	6,410	0.17	<10.0	1.0	-
2	F	48	45	3	1	3	Pleuritis	poly	+ Neurological disorder	exon2 (L110P/ E148Q)	12,530	9.32	N.A	5,800	0.14	N.A	0.5	-
3	M	40	28	12	2-3	4-7	Peritonitis Pleuritis	poly	+	exon2 (L110P/ E148Q)	10,930	1.27	189.7	6,480	0.10	<10.0	1.0	-
4	M	25	25	0.2	0.5	3	Pleuritis	poly	+	exon2 (L110P/ E148Q) exon3 (P369S/ R408Q)	30,400	10.64	844.4	4,610	0.02	<10.0	1.5	-
5	M	47	25	22	2	3	Peritonitis	poly	+	exon5 (S503C/-)	14,660	1.97	24.5	12,030	0.18	<10.0	3.5	+

Age: Age at diagnosis, Onset: Age at first time of FMF clinical feature, Delay: Delay in diagnosis of FMF, Fre: Frequency, Dur: Duration

curred occasionally, and there were no signs of meningitis.

He was admitted to another hospital at the age of 47, and was examined by enhanced computed tomography, gallium scintigraphy, and upper and lower gastrointestinal fiberscope. However, no abnormality was detected. Therefore, he was referred to our department for further examination. Physical examination was unremarkable. He had high acute phase reactants (CRP, 1.97 mg/dL; SAA, 24.5 μg/mL) and leukocytosis (WBC, 14,600/μL) during the febrile attacks, whereas other laboratory data including urinalysis revealed no abnormal findings. An *MEFV* analysis showed a heterozygote S503C mutation in exon 5. Because his recurrent fever occurred with or without nausea, he was diagnosed with an incomplete type of FMF. He was treated with colchicine, which markedly reduced the number of febrile attacks but did not completely eliminate them. The dose of colchicine was gradually increased to 3.5 mg/day.

The clinical features of the five patients with FMF are summarized in Table 1. The mean age at the time of diagnosis was 42.6 years, and the mean period between disease onset and disease diagnosis was 14.0 years. No patient had a family history suggesting FMF, nor were they children of consanguineous marriages. *MEFV* mutations were detected in all patients, with a heterozygote mutation in two patients and compound heterozygote mutations in three. These mutations included: M694I (exon 10), E148Q and L110P (exon 2), P369S and R408Q (exon 3), and S503C (exon 5). *MEFV* genetic analysis was approved by the Ethics Committee of Nagasaki Medical Center (No. 21003, 2009). A diagnosis of FMF was made when the patient had one or more of the major criteria, or two or more of the minor Tel-Hashomer criteria (6). The diagnostic criteria of FMF in five patients are shown in Table 2. Based on these criteria, the patients were divided into two groups: typical FMF (n=1) and incomplete FMF (n=4). The average period from pretreatment to posttreatment was 46 days.

All patients suffered from self-limited, recurrent bouts of fever with a period varying from bi-weekly to quarterly. In addition to periodic fever, three had abdominal pain suggesting the existence of peritonitis, two had chest and/or back pain indicative of pleuritis, five had clinically diagnosed polyarthralgia, and four had headache. One patient experienced convulsions and reduced consciousness upon febrile attacks, leading to a diagnosis of aseptic meningitis. Colchicine resistance was shown in one patient.

Elevated levels of CRP were noted in all patients, and leukocytosis was observed in four during febrile attacks; we did not measure the levels of other inflammatory cytokines. No clinical features of amyloidosis such as cardiomegaly, hepatomegaly, or proteinuria were found in any cases. Upper gastrointestinal endoscopy and total colonoscopy were performed in all cases, and no evidence of amyloidosis was found by either observation or biopsy.

Table 2. Criteria for the Diagnosis of FMF in All Five Patients.

Case		1	2	3	4	5
Major Criteria						
Typical attacks of:						
1	periotonitis (generalized)	+	-	-	-	-
2	Pleurisy (unilateral) or Pericarditis	-	-	-	-	-
3	Monoarthritis (Hip, Knee, or Ankel joint)	-	-	-	-	-
4	Fever alone	-	-	-	-	-
5	Incomplete abdominal attack		-	-	-	-
Minor Criteria						
Incomplete attacks involving either or both of the following sites						
1	Chest	-	+	+	+	+
2	joint	-	+	+	+	+
3	Exertional leg pain	-	-	-	-	-
4	Response to colchicine	+	+	+	+	-
Type of FMF		Complete	Incomplete	Incomplete	Incomplete	Incomplete

Definitive diagnosis: 1 major criterion or 2 minor criteria.

Typical attacks are defined as recurrent (>/=3 of the same type), febrile (rectal temperature of 38°C (100°F) or higher), and short (lasting between 12 hours and 3 days).

Incomplete attacks are defined as painful and recurrent, differing from typical attacks in 1 or 2 features, as follows:

The temperature is normal or lower than 38°C (100°F).

The attacks are longer or shorter than specified (but no shorter than 6 hours or longer than a week).

No signs of peritonitis are recorded during the abdominal attacks.

The abdominal attacks are localized.

The arthritis is in joints other than those specified (hip, knee, or ankle).

Discussion

FMF is a disease characterized by periodic fever, serositis, and synovitis (1). In the present study, we identified five Japanese patients with FMF. According to the commonly used Tel-Hashomer criteria (6), one of these patients carrying an *MEFV* exon 10 mutation was diagnosed with typical FMF, while the remaining four patients with *MEFV* non-exon 10 mutations were diagnosed with incomplete FMF. No laboratory tests specific for FMF are available (7); however, all five patients showed increased acute phase reactants, such as CRP, during their febrile episodes. A complete response to colchicine for preventing febrile attacks was demonstrated in all five patients, although the colchicine response was slightly reduced during the 2-year treatment in one patient with the *MEFV* S503C exon 5 mutation. Clinical manifestations and courses of FMF patients with the S503C mutation have rarely been reported (8), so further investigations are necessary to identify the clinical characteristics and therapeutic responses of FMF patients with *MEFV* exon 5 mutations including S503C.

One of the most striking features of the patients in our report is the advanced age of their FMF diagnosis. The typical interval between the first FMF symptoms and the start of colchicine treatment was around 12 years, during which time uncontrolled inflammation might have caused amyloid A (AA) amyloidosis (9). This is the most important factor determining the prognosis of FMF. However, although both the diagnosis and therapeutic intervention were delayed in our patients, no clinical symptoms or findings suggestive of AA amyloidosis were identified. Indeed, our survey of Japanese FMF patients reported frequencies of AA amyloidosis of 3.6% (10), which is lower than that seen in Mediterranean populations (11). We did not observe *MEFV* genotypes including M694V, the risk allele for amyloidosis (12), in our five Japanese cases of FMF, which may have partly contributed to the protective effects against amyloidosis.

Another observation of our case report suggests that *MEFV* non-exon 10 polymorphisms may be responsible for or associated with additional clinical manifestations that do not meet the typical FMF symptoms (13, 14), including aseptic meningitis. Various nervous system findings have been reported in the course of FMF; however, these findings are rare and have usually been documented as case reports. Neurological involvements associated with FMF include optic neuritis, demyelinating lesions, posterior reversible encephalopathy syndrome, and recurrent aseptic neuritis (15-17). Headaches were common in the current case report, occurring in four out of five patients, all of whom had *MEFV* non-exon 10 mutations and an incomplete FMF phenotype. Because colchicine treatment eradicated the headache in these patients in addition to the febrile attacks, headache could therefore be a symptom of recurrent aseptic meningitis.

The main limitation associated with the current case report was the small number of patients from a single institute and thus some possible bias, such as with patient selection.

Additionally, we did not perform either a cerebrospinal fluid analysis or brain MRI in any of the patients. Furthermore, it is conceivable that the coexistence of headache and *MEFV* non-exon 10 polymorphisms may have been incidental. However, the headaches all resolved after colchicine treatment, indicating that they could have been a true clinical manifestation of FMF.

Recently, more case reports of FMF patients have been published in Japan. Ogita et al. (18) recently reported seven Japanese cases of FMF which all carried *MEFV* mutations and responded well to colchicine treatment. Kinoshita et al. (19) presented a case of Mollaret meningitis with an *MEFV* mutation, which showed a similar clinical course to our case 2. The authors suggested that FMF should be included in the differential diagnosis of recurrent meningitis.

In conclusion, we herein described our clinical evaluation of Japanese patients with FMF. Although the central nervous system is rarely affected in patients with FMF, neurological involvement such as aseptic meningitis is possible in those with an incomplete FMF phenotype. In our cases, most patients were controlled by colchicine treatment; therefore, early diagnosis and therapeutic intervention are warranted even in Japanese patients. This treatable disease should not be left undiagnosed because severe complications, such as amyloidosis, can sometimes occur. Therefore, special efforts should be made to diagnose FMF, even for uncommon ethnic backgrounds including Japan.

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

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