Table 5. Allele frequencies of *SAA1* gene polymorphisms in typical and incomplete FMF patients.

	FMF criteria		*p* value
	Typical	Incomplete	
	2n = 92(%)	2n = 74(%)	
Allele at *SAA1* locus			
1.1	16(17.4)	20(27.0)	$\chi^2 = 3.733$ $p = 0.155$
1.3	44(47.8)	37(50.0)	
1.5	32(34.8)	17(23.0)	
Alleles at -13C/T *SAA1*			
T	51(55.4)	42(56.8)	$\chi^2 = 0.029$ $p = 0.865$
C	41(44.6)	32(43.2)	

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Table 6. Number of *MEFV* gene mutations and *SAA1* gene polymorphisms in FMF patients.

	Number of mutations		*p* value
	0~1 mutations	≧2 mutations	
	2n = 60(%)	2n = 106(%)	
Allele at *SAA1* locus			
1.1	11(18.3)	25(23.6)	$\chi^2 = 0.955$ $p = 0.620$
1.3	29(48.3)	52(49.1)	
1.5	20(33.3)	29(27.4)	
Alleles at -13C/T *SAA1*			
T	33(55.0)	60(56.6)	$\chi^2 = 0.040$ $p = 0.841$
C	27(45.0)	46(43.4)	

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and that FMF may not be a pure autosomal recessive disease due to the loss of protein function [21]. One explanation is that subjects having a single *MEFV* mutation may develop an FMF phenotype in the presence of other inflammasome-related genes or in the presence of other environmental factors [22]. Therefore, the role of potential modifier genes and polymorphisms within these gene families should be assessed in conjunction with genotype-phenotype association studies. Polymorphisms in genes associated with the inflammasome pathway can affect the development of FMF [5]. For example, TLR2 polymorphisms may be an important factor in the susceptibility of FMF [23,24].

In this study, we investigated the *SAA1* and *IL-1β* gene polymorphisms in Japanese patients with FMF. There was no significant difference in *IL-1β-511* (C/T) or *IL-1Ra* VNTR polymorphisms between FMF patients and healthy subjects in accord to the previous report [25]. However, we demonstrated that *SAA1* gene polymorphisms, which are attributed to AA amyloidosis, might be also responsible for susceptibility to FMF. It is clear that genotypes at the *SAA1* locus are associated with an increased susceptibility to AA amyloidosis [26]. However, the contribution of these genotypes to the occurrence of non-amyloid, inflammatory disease has not been elucidated. In this study, we investigated the allele frequencies of *SAA1.1* and -13 (C/T) polymorphisms of the *SAA1* promoter region in Japanese patients with FMF. Our data demonstrated that the -13T allele polymorphism was a major risk factor and that the *SAA1.1* allele was protective for the occurrence of FMF in Japanese case-control studies.

The presence of 2 single-nucleotide polymorphisms (SNPs) within exon 3 of the *SAA1* gene, 2995 C/T and 3010 C/T, defined 3 haplotypes that corresponded to the *SAA1.1*, *SAA1.3*, and *SAA1.5* isoforms [26]. In Japanese patients with RA, homozygote expression of the *SAA1.3* allele was a proven risk factor, whereas *SAA1.1* appeared to be protective for AA amyloidosis [27]. In contrast, a strong positive association with *SAA1.1* has been established in Caucasian patients with amyloidosis secondary to juvenile idiopathic arthritis and FMF [28–30]. Moriguch *et al.* identified another *SAA1* SNP, the -13T/C SNP in the 5′-flanking region of the *SAA1* gene [17]. They observed the -13T allele was associated with AA amyloidosis, and associated with the *SAA1.3* allele in Japanese RA patients [17]. Interestingly, a polymorphism in the *SAA1* promoter -13T allele was found to be significantly associated with increased AA amyloidosis risk in both populations and to be in linkage disequilibrium with *SAA1.1* and *SAA1.3* in Caucasian and Japanese patients, thus apparently explaining the previous discrepancy [31–35]. Functional studies have demonstrated that the -13T allele is responsible for a higher transcriptional rate [36]. However, this did not result in higher serum levels of SAA, possibly due to increased proteolytic processing rates of *SAA1.1* and *SAA1.3* compared to *SAA1.5* [37]. The mechanisms by which the -13T allele predisposes to FMF remains to be unraveled and many possibilities have been suggested.

The overproduction of IL-1β, induced by NLRP3 inflammasome activation, is responsible for a variety of autoinflammatory syndrome including FMF. The NLRP3 inflammasome has emerged as a critical cytosolic sensor for a number of endogenous mediators, including amyloid proteins [6]. Recent studies indicated that SAA activates the NLRP3 inflammasome in a cathepsin B and $P2X_7$-dependent manner, resulting in the secretion of mature IL-1β [10]. The accumulation of newly formed AA amyloid fibrils and aberrant processing of SAA is relevant to AA amyloidogenesis [38]. Therefore, in subjects with AA amyloidogenic genetic factors, such as -13T allele, the presence of SAA-derived AA amyloid fibrils may implicate the NLRP3 inflammasome activation pathway, which is thought to be relevant to the pathogenesis of FMF. Jeru *et al.* demonstrated that the *SAA1* genotype influenced the severity of FMF and disease susceptibility through a negative selection process, providing new insights into the role of *SAA1* in the pathophysiology of FMF [39]. Assuming that *SAA1* gene polymorphisms induce the formation of AA amyloid fibrils, this suggests that the polymorphisms may be associated with the NLRP3 inflammasome activation process and susceptibility to FMF. These findings may provide insights into modifier factors, other than *MEFV*, in the development of FMF.

The gender discrepancy (female dominant in incomplete FMF) seen in the present study may result from hormonal or associated environmental factors, which generate a disease of atypical or milder severity in female. For example, the risk for developing amyloidosis had been shown to be higher in male patients with FMF [40,41]. These findings suggest that clinical variability observed in FMF may be party attributed to the influence of environmental factors including gender. The main limitations of the study are its localization to a certain country, and a limited number of patients.

Table 7. Frequencies of *SAA1* -13C/T, *SAA2*, *IL1β* -511 genotypes in Japanese patients with FMF and frequencies of *SAA1* -13C/T, *SAA2*, *IL1β* -511 genotypes in healthy subjects.

Frequencies of *SAA1* -13C/T, *SAA2*, *IL1β*-511 genotypes in Japanese patients with FMF

Locus	Genotype	Observed number(%)	Expected number[a]	*p* value
SAA1 -13C/T	C/C	13(15.7)	16.1	$\chi^2 = 1.292$ $p = 0.256$
	C/T	47(56.6)	40.9	
	T/T	23(27.7)	26.1	
SAA2	A/A	62(74.7)	61.6	$\chi^2 = 0.007$ $p = 0.932$
	A/G	19(22.9)	19.8	
	G/G	2(2.4)	1.6	
IL1β -511	C/C	27(32.5)	28.3	$\chi^2 = 0.144$ $p = 0.704$
	C/T	43(51.8)	40.3	
	T/T	13(15.7)	14.3	

Frequencies of *SAA1* -13C/T, *SAA2*, *IL1β*-511 genotypes in healthy subjects

Locus	Genotype	Observed number(%)	Expected number[a]	*p* value
SAA1 -13C/T	C/C	67(33.5)	69.6	$\chi^2 = 0.384$ $p = 0.535$
	C/T	102(51.0)	96.8	
	T/T	31(15.5)	33.6	
SAA2	A/A	163(81.5)	162.9	$\chi^2 = 0.104$ $p = 0.747$
	A/G	35(17.5)	35.2	
	G/G	2(1.0)	1.9	
IL1β -511	C/C	59(29.5)	59.4	$\chi^2 = 0.001$ $p = 0.978$
	C/T	100(50.0)	99.2	
	T/T	41(20.5)	41.4	

[a]Expected genotype frequencies based on observed allele frequencies and assuming Hardy-Weinberg equilibrium.

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In occlusion, this study shows a significant prevalence of the -13T allele in Japanese patients with FMF. This comparative case-control study demonstrated that the *SAA1* gene polymorphisms might affect susceptibility to FMF, which is presumed to be a monogenic disease. Further studies are required to determine the impact of *SAA1* gene polymorphisms and the occurrence of FMF in large studies in different geographic areas.

Ethics approval

This study was conducted with the approval of the ethical committees of Nagasaki Medical Center.

Author Contributions

Conceived and designed the experiments: KM KA JM HI AK RU YN . Performed the experiments: YJ YM MY. Analyzed the data: KM M. Nakamura YM. Contributed reagents/materials/analysis tools: SH YI TK M. Nakashima YF FN KE HF TN. Wrote the paper: KM M. Nakamura YM.

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INTERNAL MEDICINE

□ CASE REPORT □

Familial Mediterranean Fever Occurring in an Elderly Japanese Woman with Recent-onset Rheumatoid Arthritis

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Abstract

A 60-year-old woman with a two-year history of rheumatoid arthritis (RA) developed recurrent two- to three-day attacks of fever (>38℃) accompanied by monoarthritis of the right hip joint. The first attack occurred two months after beginning anti-tumor necrosis factor-α therapy. Since a diagnosis of infectious arthritis was suspected, the therapy was discontinued. Thereafter, the patient repeated similar episodes; however, oral colchicine effectively controlled the attacks. The patient was diagnosed to have familial Mediterranean fever (FMF). The clinical manifestations of FMF mimic infectious complications during anti-RA therapy. Clinicians should therefore consider the possibility of FMF development in RA patients exhibiting recurrent febrile attacks.

Key words: familial Mediterranean fever, rheumatoid arthritis, *MEFV*, colchicine, infectious arthritis

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive, hereditary, autoinflammatory disorder characterized by recurrent one- to three-day attacks of fever and paroxysmal serositis, usually involving the peritoneum, pleura and synovial joints (1, 2). This disease is prevalent in individuals of Mediterranean descent, such as non-Ashkenazi Jews, Armenians, Turks and Arabs, and is quite rare in Japan. Approximately 90% of all cases occur before 20 years of age. Almost all FMF patients carry mutations in the pyrin-encoding gene *MEFV* on chromosome 16p13.3 (3, 4). Mutated forms of pyrin proteins may be involved in alterations of inflammatory processes that ultimately result in the uncontrolled expression of the potent proinflammatory cytokine, interleukin-1β. In turn, overexpression of IL-1β leads to dysregulated neutrophil activation and bursts of systemic inflammation (5). Recently, the presence of an association between *MEFV* mutations and the occurrence of rheumatic diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and ankylosing spondylitis, has been suggested (6-8). Two studies have shown that RA patients carrying *MEFV* mutations have higher severity scores than non-carriers (9, 10). Nevertheless, no cases of coexisting RA and FMF have hitherto been reported. We herein report a case of FMF occurring in an elderly Japanese woman with a two-year history of RA who was receiving immunosuppressive anti-RA therapy.

Case Report

In February 2007, a 60-year-old woman was diagnosed to have early RA at our outpatient clinic. At that time, a physical examination revealed five swollen and six tender small joints, including both wrists. She also complained of morning stiffness in and around these joints lasting longer than one hour. These symptoms had persisted for two months. Plain radiographs of the hands showed evidence of bone erosion and joint space narrowing. Given these findings, the patient met five of the seven 1987 American College of Rheumatology criteria for RA diagnosis. Both the serum C-reactive protein (CRP) levels and the erythrocyte sedimentation rates were high. The patient was also positive for anti-

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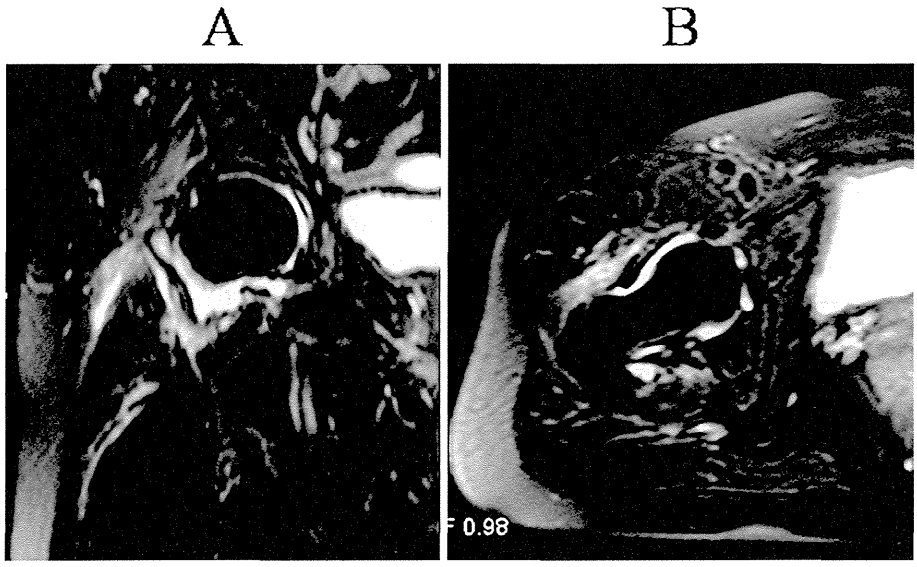

Figure. Magnetic resonance imaging scans obtained during the patient's first febrile attack. Fat suppression T2-weighted (FS-T2W) images in the coronal (A) and axial (B) planes show high signals in the right hip joint. The findings suggest the presence of joint effusion and thickened synovium. High signals are also seen in the soft tissues around the joint, thus reflecting inflammatory changes.

cyclic citrullinated peptide antibodies (57 IU/mL); however, she exhibited a negative result for rheumatoid factor. The disease activity score for 28 joints (DAS28) was 5.1 and Steinbroker's stage was II. The patient carried two copies of shared epitope-positive HLA-DRB1 alleles (*0101/*1001). Following treatment with 8 mg/week of methotrexate (MTX), she achieved low disease activity.

In April 2009, anti-tumor necrosis factor-α (anti-TNFα) therapy with infliximab (3 mg/kg) was initiated in combination with MTX because the patient's RA had deteriorated (DAS28: 6.05). She responded well to this therapy: the DAS 28 score fell to 2.11 immediately before the third infusion. Two months later, the patient visited our hospital due to a high fever of 39℃ and severe pain in the right hip joint. Neither pulmonary complications nor abdominal symptoms were observed. The white blood cell (WBC) count was elevated with neutrophilia (12,650/μL), and the level of CRP was also high (10.8 mg/dL). The serum levels of hepatic aminotransferases, blood urea nitrogen and albumin were within the normal ranges. Tests for serum endotoxin, β-D glucan and procalcitonin were negative. Neither renal dysfunction nor proteinuria were observed. There was no radiographic evidence of erosion or destructive involvement of the hip joint. Magnetic resonance imaging scans of the hip joint revealed massive amounts of fluid and synovial hypertrophy (Figure). Joint aspiration performed during the attack revealed sterile pyogenic synovial effusion without calcium pyrophosphate deposition or uric acid crystals. Cultures did not produce any bacteria. The patient's hip joint pain and a high fever >38℃ continued for three days, then subsided and disappeared. Although the origin of the fever was unknown, infliximab therapy was discontinued. Alternative anti-RA treatment consisting of 1 mg/day of tacrolimus and MTX was introduced, and the patient remained in remission.

In September 2009, the patient developed recurrent two-day fever episodes (>38℃) accompanied by severe pain in the right hip joint. The WBC count and CRP level both increased during these attacks. Since a diagnosis of FMF was suspected, colchicine (1 mg/day) was administered, and the attacks were effectively controlled. This therapy was continued until August 2010. In May 2011, the patient once more experienced recurrent attacks of high fever (>38℃) and severe right hip joint pain lasting two days; as before, she responded very favorably to colchicine. Considering the typical feverish attacks accompanied by monoarthritis of the hip joint, as well as the adequate response to colchicine, the patient fulfilled one major and one minor criterion of the Tel Hashomer criteria for a diagnosis of FMF (11). A definitive diagnosis of FMF was therefore given to the patient. The patient exhibited no cutaneous, mucous, eye, or neurological involvement. Neither xerostomia nor dry eye were observed. The patient did not complain of gastrointestinal or respiratory symptoms. There was no laboratory evidence suggesting that the patient had developed renal dysfunction, hepatic impairment or a hematological disorder. A urinalysis by dipstick showed no abnormal findings. Therefore, we excluded the possibility that the patient's recurrent febrile attacks were due to autoinflammatory diseases, including Sjögren's syndrome, Behçet's disease, systemic lupus erythematosus, vasculitis and inflammatory bowel disease. In addition, the patient presented with no clinical findings that raised the suspicion of lymphoma, such as lymphadenopathy, lymphopenia, splenomegaly or cryoglobulinemia.

The patient denied having had any recurrent fever episodes prior to the first visit to our clinic. According to an

interview regarding the patient's family health history, none of her first-degree relatives had experienced typical FMF symptoms. A mutation analysis was performed by sequencing all exons of the *MEFV* gene (exons 1-10) as described elsewhere (12). We found that the patient was heterozygous for the E148Q allele in exon 2. Until the time of submission, the daily administration of colchicine was continued without any attacks of fever.

Discussion

Considering that the attacks of fever and hip joint monoarthritis occurred within the first two months of infliximab therapy, we suspected a diagnosis of infectious arthritis, which led to discontinuation of this therapy. Anti-TNFα therapy increases the risk of septic arthritis in RA patients compared with nonbiological disease-modifying antirheumatic drugs (13, 14). Since septic arthritis is potentially life-threatening, this decision was inevitable. However, consideration should be given to the possibility of FMF development in RA patients exhibiting recurrent attacks of fever, although it is unclear whether the coexistence of FMF and RA is a mere coincidence or whether there is an association between these two diseases. FMF manifestations can mimic many common infectious diseases. We believe that a therapeutic trial with colchicine is justified in such cases. It has recently been shown that anti-TNFα agents are effective in treating colchicine-resistant FMF cases (15). Our patient, however, developed the clinical symptoms of FMF during infliximab therapy. The role of TNFα in FMF pathogenesis remains to be clarified.

It is now known that the *MEFV* gene is associated with several rheumatic diseases, not only FMF (6-8). Coexistence of systemic lupus, JIA, Sjögren's syndrome, and polymyositis with FMF has been reported (12, 16-18). As for RA, carriage of *MEFV* mutations, and the E148Q mutation in particular, has been reported to be an independent modifier for clinical manifestations in Israeli patients (9). In a Turkish cohort, *MEFV* mutations appeared to be an aggravating factor for RA severity (10). Conversely, no significant associations between the presence of these mutations and the development of RA or RA-related amyloidosis were found in a Japanese population (19). It is uncertain whether differences in the genetic backgrounds of these ethnic groups are responsible for this discrepancy. The present patient experienced her first FMF episode two years after the onset of RA. When RA patients develop recurrent fevers and monoarthritis in large joints such as the hip, ankle and knee, then the concurrence of FMF should be considered as a possible cause.

FMF patients experiencing disease onset after 60 years of age are extremely rare (20-22). The cause of late-onset FMF is unclear; however, heterozygosity of *MEFV* mutations may contribute to this phenotype. The present patient carried the heterozygous E148Q allele in the *MEFV* gene. Since FMF has traditionally been considered an autosomal-recessive disease, a heterozygote is expected to be a carrier and to lack the clinical phenotypes of FMF. However, several research groups have suggested that carriers of one *MEFV* mutation may have a tendency to develop certain manifestations due to having an increased baseline of inflammation and may develop rheumatic diseases more often than 'healthy' populations (6, 23-25). Recently, two groups reported the existence of a significant subset of FMF patients who are carriers of only one *MEFV* mutation, thus suggesting that having the heterozygous mutation is sufficient to express the typical clinical features of FMF (26-28). In another study, the clinical presentations of patients with recurrent fever and only one *MEFV* mutation appeared to resemble those of homozygous patients, and most of the cases required colchicine treatment (29). In either case, mutation analyses of *MEFV* and therapeutic trials with colchicine should be considered in patients exhibiting recurrent febrile attacks, even among those over 60 years of age.

Whether the E148Q allele in the *MEFV* gene is a true disease-causing mutation or a benign polymorphism remains controversial. The E148Q allele appears to confer an inflammatory phenotype in Turkish individuals (30). In a Greek population, the E148Q allele was found to be significantly more frequent in FMF patients than in healthy controls (31). These findings suggest that the E148Q allele is a disease-causing *MEFV* mutation. In a Jewish population, however, the frequency of the E148Q allele was similar between FMF patients and healthy controls, favoring the concept of a non-causative role (32, 33). Tomiyama et al. showed that the E148Q and M694I alleles are most frequently detected in Japanese patients, although the impact of the E148Q allele on FMF manifestations is low (34). Nevertheless, the present patient developed the FMF phenotype in her sixties. There may be an unknown factor or event capable of triggering the disease through interactions with IL-1β-related inflammatory pathways.

Fortunately, our patient shows no evidence of developing serious complications to date, and her RA remains in remission. Since inflammation can persist, even during attack-free periods, in many FMF patients, providing careful monitoring of inflammatory markers and adequate control of chronic inflammation is required to prevent the development of complications such as life-threatening amyloidosis (35). Although the present patient's symptoms had been well controlled for one year, her attacks of fever returned after cessation of colchicine treatment. Daily lifelong administration of colchicine is required to prevent both attacks of fever and silent amyloid deposition (2).

In conclusion, FMF can occur in RA patients. The clinical manifestations of FMF mimic infectious complications, which can delay FMF diagnosis for many years and can occasionally subject patients to unnecessary examinations and inadequate treatments. Clinicians should therefore be aware of the possible coexistence of FMF in RA patients exhibiting recurrent febrile attacks. Conducting a therapeutic trial with colchicine is thus considered to be justified in such cases.

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

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CASE REPORT

Colchicine-responsive protracted gouty arthritis with systemic inflammatory reactions

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Abstract Acute gouty arthritis is a severe but self-limiting arthritis caused by inflammatory responses to urate crystals. Oral colchicines are effective for initial stages or prophylaxis, but generally, colchicines are ineffective for established gouty arthritis. We describe an unusual case of gouty arthritis with systemic inflammatory reactions, including high fever and polymyalgia. Refractory polyarthritis and high fever were eradicated by colchicine treatment. Genetic analysis revealed a heterozygous mutation in exon 2 of the *MEFV* gene (E148Q). This case underscores the possibility that *MEFV* gene mutations may modify the phenotype of gouty arthritis.

Keywords Colchicine · Gouty arthritis · *MEFV* gene

Introduction

Gout is the most common inflammatory arthritis and is characterized by recurrent arthritic attacks of intra-articular monosodium urate deposition [1]. Multiple lines of evidence support the hypothesis that inflammasome-related genes are disease-susceptible candidate genes for gout [2, 3].

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Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease, caused by mutations in *MEFV*, the gene encoding the protein pyrin, which can act as a regulator of inflammasome function [4]. Recent studies indicated that the *MEFV* gene is associated with other conditions apart from typical FMF and is linked to additional clinical presentations within the family of connective tissue diseases [5, 6]. Gouty arthritis and FMF rarely coexist. We describe an unusual case of gouty arthritis with systemic inflammatory reactions, including persisting high fever and protracted polyarthritis.

Case report

A 59-year-old male patient was admitted to our hospital for polyarthritis and persistent high fever (>38.5 °C). Seven years earlier, he developed recurrent episodes of polymyalgia and polyarthralgia that subsided spontaneously within a couple of weeks. There was no medical history of periodic fever among his family. His first symptoms, present 2 weeks prior to hospital admission, were symmetrical arthralgia in the wrist and elbow joints with joint swelling, which developed to polyarthralgia of the symmetrical upper and lower extremities (elbows, knees, ankles and metatarsophalangeal joint). He visited the local clinic because of the persistent polyarthralgia and accompanying polymyalgia and high fever. He was diagnosed with palindromic rheumatism and treated with steroids (prednisolone 10 mg/day). However, joint swelling and high fever persisted despite this treatment. He was referred and admitted to our hospital for further examinations.

Physical examination of the patient showed a body weight of 70.0 kg, blood pressure of 126/70 mmHg, body temperature of 38.6 °C and normal chest and abdomen.

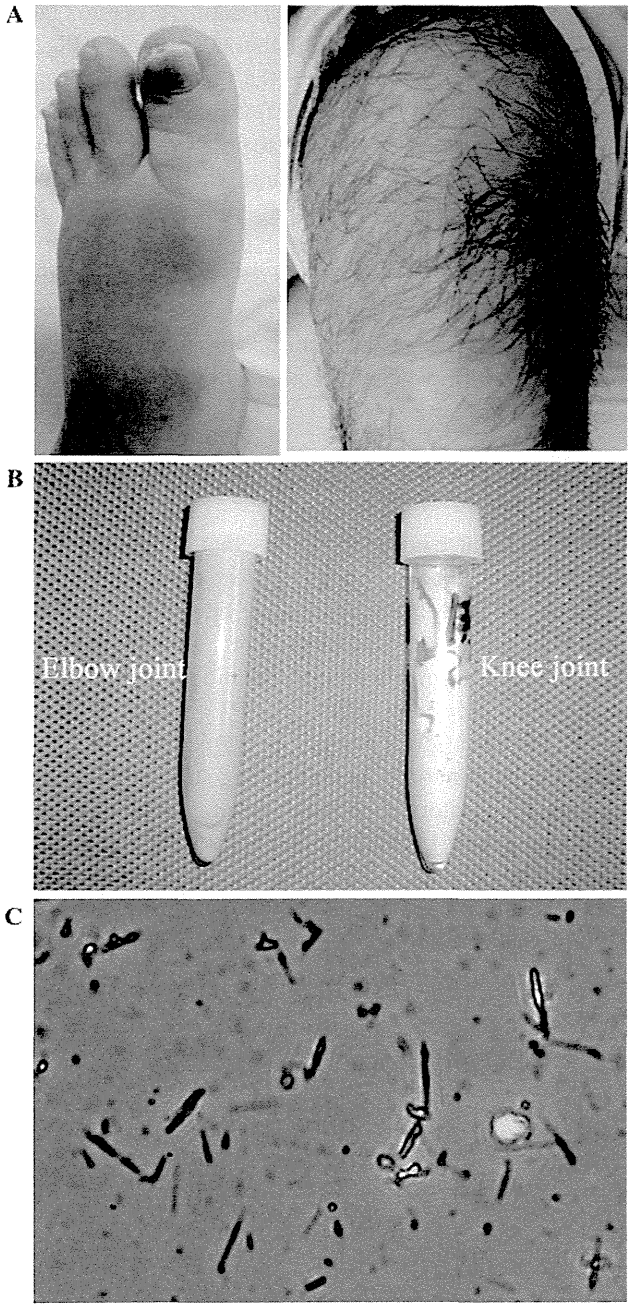

Fig. 1 **a** Acute gouty arthritis over the left knee and right first metatarsophalangeal joints seen in the present case. **b** Synovial fluids from the inflamed knee and elbow joints, demonstrating the color of "urate milk". **c** Numerous needle-shaped crystals in synovial fluids from the knee joint under phase-contrast microscopy

Table 1 Laboratory findings

Peripheral blood		Serological tests	
Red blood cells	366 × 10^4/μl	sL-2R	691 IU/ml (< 460)
Hemoglobin	12.9 g/dl	C-reactive protein	24.7 mg/ml (< 0.30)
White blood cells	15,000/μl	Erythrocyte sedimentation rate	94 mm/h
Neutrophil	72.7 %	IgG	1990 mg/dl (900–2,000)
Eosinophil	2.4 %	Anti-nuclear Ab	(–)
Monocyte	7.3 %	Anti-CCP Ab	(–)
Lymphocyte	17.4 %	RF	(–)
Platelet	33.3 × 10^4/μl	Urinalysis	
Blood chemistry		pH	6.0
Total protein	7.5 g/dl	Protein	(–)
Total bilirubin	1.1 mg/dl	Glucose	(–)
Glutamic-oxaloacetic transaminase	24 IU/l (7–33)	Occult blood	(–)
Glutamic-pyruvic transaminase	38 IU/l (5–30)	Sediment	np
Lactate dehydrogenase	178 IU/l (260–480)	Synovial fluids	
Alkaline phosphatase	370 IU/l (80–250)	IL-1β (knee)	332 pg/ml
Creatinine kinase	29 IU/l (60–160)	IL-1β (elbow)	252 pg/ml
Total cholesterol	139 mg/dl		
Blood urea nitrogen	17.5 mg/dl		
Creatinine	0.84 mg/dl		
Uric acid	7.4 mg/dl		
Ferritin	1763 mg/dl		
Procalcitonin	0.18 ng/ml		

RF rheumatoid factor, *Anti-CCP Ab* anti-cyclic citrullinated peptide antibody, *sIL-2R* soluble interleukin-2 receptor

Acute synovitis was noted over the bilateral elbow, wrist, knee, ankle and 1st metatarsophalangeal joints (Fig. 1a). The bilateral elbow and knee joints had bursitis. Blood analysis showed elevated white blood cell counts (15,000/mm^3), high levels of C-reactive protein (24.7 mg/dl), accelerated ESR (94 mm/h), and elevated serum uric acid (7.4 mg/dl). Auto-antibodies were not detected and blood culture was negative (Table 1). To clarify the etiology of the arthritis, synovial fluids were aspirated from the left knee and right elbow joints (Fig. 1b). The fluid was white with some sedimentation. Synovial fluid analysis revealed many needle-shaped crystals under phase-contrast microscopy (Fig. 1c). Monosodium urate (MSU) crystals were considered. Microbacterial culture was performed, but no pathogen was observed. Synovial fluids from knee and elbow joints were analyzed for interleukin (IL)-1β using IL-1β-specific ELISA. Increased levels of IL-1β were confirmed in both synovial fluids (knee joint 332 pg/ml; elbow joint 252 pg/ml, Table 1). Thus, a diagnosis of gouty polyarthritis without evidence of infectious disease was suspected. However, the high fever continued despite

the treatments consisting of nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids (prednisolone 5 mg/day) for a week. We performed *MEFV* gene analysis because of the atypical manifestations seen in the present case under the patient's informed consent, demonstrating a heterozygous mutation of exon 2 (E148Q) of the *MEFV* gene (Fig. 2). Soon after colchicine treatment (0.5 mg/day), there was a dramatic reduction of the high fever and polyarthralgia (Fig. 3). The daily colchicine therapy relieved febrile attack and synovitis. After discharge, the patient had been treated with a uric acid-lowering drug (benzbromarone 100 mg/day), which controlled his serum uric acid levels within normal range (4–5 mg/dl). However, high fever, polyarthralgia and polymyalgia relapsed when he discontinued colchicine at his discretion. This febrile attack disappeared promptly after the readministration of colchicine.

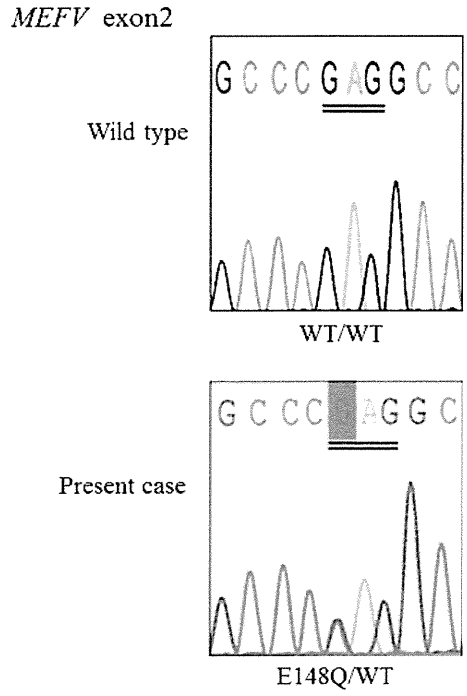

Fig. 2 *MEFV* gene analysis in a healthy control (wild type) and in the present case, E148Q heterozygous mutation, in which the G to C transition in codon 148, converting a glutamic acid (E) to glutamine (Q), was demonstrated in the present patient

Discussion

Epidemiological evidence suggests that <10 % of hyperuricemia patients develop gout, indicating that other genes unrelated to urate metabolism may contribute to disease susceptibility [7]. Accumulated reports have demonstrated that MSU crystal-mediated inflammation is a paradigm of innate immunity and that NLRP3 inflammasome is involved in gout development [8]. Furthermore, functional NLRP3 gene mutations are promising susceptibility genes for autoinflammatory hereditary periodic fever syndromes, including gout [9]. One of the characteristic features of acute gouty attack is that it is a self-limiting arthritis without high fever, regardless of treatment [10]. The present patient fulfilled the criteria for gouty arthritis, according to the presence of uric acid crystals in his

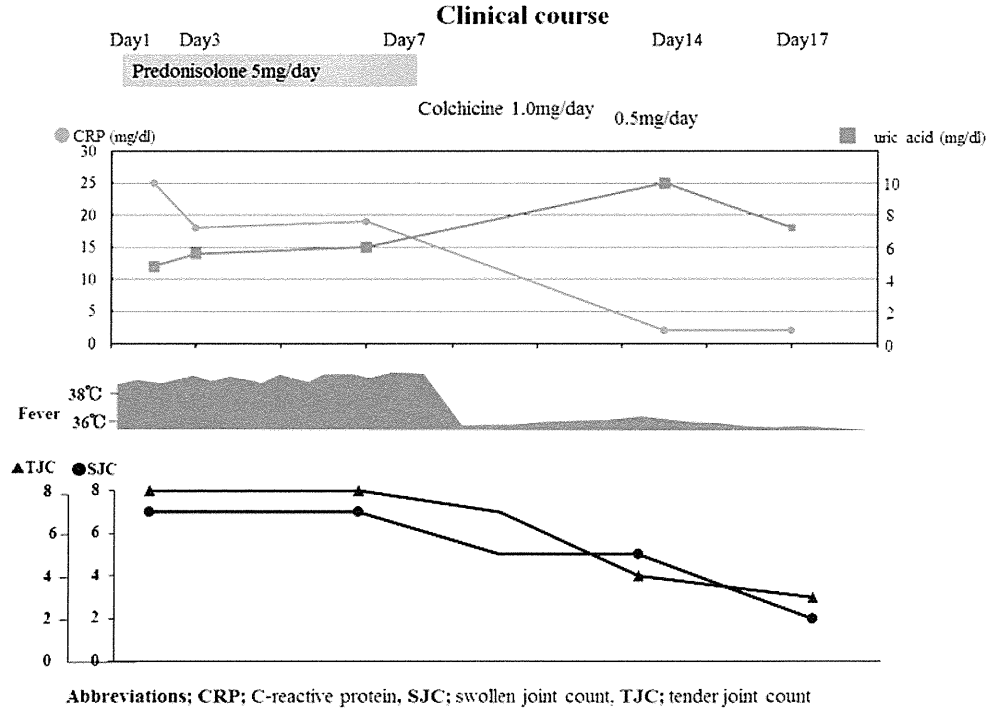

Fig. 3 Clinical course in the present case

Abbreviations; CRP; C-reactive protein, **SJC;** swollen joint count, **TJC;** tender joint count

synovial fluids. However, presentation of the current case was unusual, since the patient suffered from sustained high fever, and polymyalgia in addition to protracted arthritis. For treatment of acute gouty arthritis, NSAIDs are the first line of therapy, and corticosteroids are an additional alternative therapy [11]. Colchicine is generally not used as the first line of therapy, due to lesser effectiveness against established gouty arthritis [11]. Administration of colchicine immediately eliminated all the patient's proinflammatory symptoms, and mutation analysis showed that he carried a heterozygous mutation in exon 2 of the *MEFV* gene (E148Q). The *MEFV* gene encodes a protein called pyrin. Although the precise function of pyrin is not fully understood, it has a key role in the regulation of inflammasome activity and pro-IL-1β processing [12]. Pyrin is expressed predominantly in neutrophils, and mutations of the *MEFV* gene may be linked to abnormalities of neutrophil functions [13], which are related to the pathogenesis of FMF and gout. It is possible that the *MEFV* mutation contributed to the atypical clinical manifestations of gouty arthritis, such as persisting fever and polyarthritis, seen in the patient. However, we could not confirm the uric acid crystals that are phagocytosed by neutrophils or monocytes, the typical findings of gouty arthritis. Additionally, the use of colchicine in our case successfully silenced the febrile attack and polyarthritis, and the discontinuation of colchicine resulted in the prompt recurrence of febrile attack, despite of the normalization of serum uric acid levels. Therefore, we presumed that the arthropathy seen in the current case was FMF-related joint involvement, rather than gouty arthritis.

FMF is a common autosomal recessive inherited periodic fever syndrome [4]. Attacks of FMF last 1–3 days and are characterized by polyserositis and synovitis. Most of the disease-causing mutations in FMF are located on exon 10 of the *MEFV* gene [14]. E148Q is one of the *MEFV* mutations seen in FMF. Recently, patients with heterozygous *MEFV* mutations, especially genetic variations in exon 1, 2 and 3, have been shown to present with distinct clinical manifestations not typical to FMF, and that colchicine treatment improved the recurrent episodes of musculoskeletal symptoms [5, 6, 15]. These reports show that the *MEFV* gene is associated with disorders other than FMF, and may be linked to additional clinical presentations and modifications of inflammatory diseases. Gout is a well-defined inflammatory disease. In typical cases, acute gouty arthritis appears to be self-limiting and subsides within several days [16]. We speculated that the heterozygous mutation E148Q in the *MEFV* gene might be relevant to the modification of the clinical course of gouty arthritis in this patient. Large-scale studies for patients with unusual crystal-induced arthritis are required to clarify the relevance to *MEFV* gene mutations.

Among *MEFV* gene mutations, there is controversy as to whether E148Q is a true disease-associated mutation or simply a polymorphism [17]. A recent study demonstrated notable differences in E148Q allelic frequency between groups of healthy individuals and groups of FMF patients, or groups of palindromic rheumatism patients [18]. These data are in concordance with the previously reported over-representation of E148Q in several inflammatory disorders [19, 20].

In conclusion, gout is a common inflammatory disorder. However, when there are atypical clinical manifestations, such as high fever, protracted synovitis, and myalgia, differential diagnosis, including autoimmune or autoinflammatory diseases, is needed. It is possible that systemic manifestations seen in gouty arthritis with *MEFV* mutations might be considered as *MEFV*-associated autoinflammatory reactions, suggesting therapeutic opportunities in these conditions. Further studies are warranted to provide information on whether the genetic variations of inflammasome-related molecules could contribute to susceptibility, severity and clinical phenotype of gouty arthritis.

Conflict of interest None.

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リウマチ科，41(1)：62-70，2009

特集 リウマチ性疾患診療における日本のエビデンス

わが国における TRAPSの診断と治療*

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右田清志***
江口勝美**

Key Words：autoinflammatory syndrome, TNF-associated periodic syndrome, TRAPS, TNF, TNFRSF1A(TNFR1)

はじめに

遺伝性周期性発熱症候群であるTRAPS(TNF receptor-associated periodic syndrome)は，TNFが病態の中心と考えられている疾患である．TNFとそのレセプターであるTNFレセプター1(TNFR1, TNFRSF1A)分子との相互関係が病態に重要な役割を果たしている．本稿では，TRAPSについて不明熱の検索の結果を提示しながら臨床像を紹介するとともに，診断基準，治療法を中心に解説したい(TNFRSF1Aという表記が推奨されているが，本稿ではTNFR1と記載する)．

TRAPSの臨床像

TRAPSは，1982年にfamilial Hibernian feverとしてIrelandの家系が報告され[1]，1999年にMcDermottらが初めて疾患遺伝子を同定した遺伝性の周期性発熱症候群の一つである[2]．北欧の家系からの報告が多く，アジアでは稀な疾患と思われていたため，本邦ではあまり注目されていなかった．Hullらが，世界中の症例を検討し，その特徴をまとめ，表1のような診断基準案(diagnostic indicators)を提唱している[3]．Stojanovらの集計によると，発熱に加え，腹痛(77.1%)，筋肉痛(63.5%)，発疹(55.2%)，関節痛・関節炎(51.0%)，眼症状(48.8%)，胸膜炎(32.0%)，などが主な症状である[4]．また，心筋炎[5]，血管炎[6]，神経症状[7]など，多彩な症状も報告されている．発症年齢は平均10歳(1～63歳)，発熱期間は平均14日(2～56日)である[4]．TRAPSの生命予後を左右する二次性アミロイドーシスは，TRAPS患者の約14%に合併するが，多くが

表1 TRAPSの診断基準案

1. 6か月以上反復する炎症徴候の存在(いくつかの症状が同時にみられることが一般的)
   (1)発熱
   (2)腹痛
   (3)筋痛(移動性)
   (4)皮疹(筋痛を伴う紅斑様皮疹)
   (5)結膜炎・眼窩周囲浮腫
   (6)胸痛
   (7)関節痛，あるいは単関節滑膜炎
2. 症状が平均5日以上持続(症状は変化する)
3. グルココルチコイドに反応，コルヒチンに反応なし
4. 家族歴あり(孤発例も存在)
5. どの民族でも起こりうる

(Hullらの文献[3]より改訳引用)

* TNF receptor-associated periodic syndrome(TRAPS) in Japan : clinical characterization, pathogenesis, diagnostic criteria, and treatment.

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表2 遺伝子検索結果

Gene data(n=100)
TNFRSF1A(exon 2, 3, 4, 6, 7)：mutation(+) 4 cases(T61I：3 cases, C88Y)
MEFV：mutation(+) 42 cases(FMF：3 cases).

	E148Q	M694I	P369S	R408Q	L110P	
	E/Q	M/I				FMF
	E/E	I/I	P/P	R/R	L/L	
	Q/Q	M/M	P/P	R/R	L/P	
Other mutations						case
	E/Q	M/M	P/P	R/R	L/L	19
	E/Q	M/M	P/P	R/R	L/P	15
	E/Q	M/M	P/S	R/Q	L/L	1
	E/E	M/M	P/S	R/Q	L/L	4
Normal						
	E/E	M/M	P/P	R/R	L/L	58

表3 TRAPS孤発症例

Pt#	age/sex	TNF-α (pg/ml)	sTNFR1 (ng/ml)	sTNFR2 (ng/ml)	*TNFRSF1A* (exon 2, 3, 4)	*MEFV*
8	20M	96.1	5.6	20	mutation(−)	148(E/Q), 110(L/P)
11	51F	71.2	3.2	3.8	mutation(−)	mutation(−)
13	22F	59.0	5.5	33.5	mutation(−)	mutation(−)
15	42M	812.0	3.7	11.9	mutation(−)	mutation(−)
47	3 M	77.9	3.5	15.8	mutation(−)	369(P/S), 408(R/Q)
VAHS	19F	107.2	11.8	84.9	NT	NT
Control		11.9±6.4	1.2±1.1	3.0±1.3		

NT：not tested, VAHS：virus associated hemophagocytic syndrome

シスチン残基の突然変異である[4]．シスチン残基の突然変異によるTRAPSでは，アミロイドーシスを含め重症例が多い[3]．また，症例報告では，TRAPS症状(筋肉痛，関節痛，皮疹，胸痛など)に発熱を欠く症例(Y20H)[8]，TRAPS症状はないがアミロイドーシスが証明された症例(T50M)[8]もある．さらに，コルヒチンが効かない家族性地中海熱症例で家族性地中海熱の原因遺伝子*MEFV*とTRAPSの原因遺伝子*TNFRSF1A*の両方に突然変異を認めたoverlap症候群の報告もある[9]．

不明熱症例の検討

2004年に本邦で初めて，TRAPS患者を報告[10]した後，TRAPS疑いとして不明熱症例の相談を全国の施設から受け，症例の解析を行った．現在まで，TRAPS疑いとして紹介された症例は115例(男性52例，女性63例)である．原因遺伝子である*TNFRSF1A*遺伝子と発熱以外の症状が似ている家族性地中海熱の疾患遺伝子*MEFV*遺伝子の検索を行った．さらに，論文発表，学会発表された本邦におけるTRAPS患者を調査した．検索結果を以下に示す．

(1)遺伝子検索100例の検討では，TRAPSのhot spotである*TNFRSF1A*遺伝子のエキソン 2, 3, 4 に 4 例突然変異がみられた(表 2)．一方，家族性地中海熱の疾患遺伝子である*MEFV*遺伝子を検索したところ，42例に変異がみられた．症状と遺伝子変異の特徴から，3 例は家族性地中海熱と診断した(表 2)．

(2)*TNFRSF1A*遺伝子変異はなかったが，臨床症状と血清中のサイトカイン値から，TRAPS孤発例と考えられる症例が 5 例あった(表 3)．これらをTRAPSと診断するかは，議論の余地があると思われる．この問題については，TRAPSの診断基準の項で後述する．

(3)本邦におけるTRAPS患者数は，論文発表[10)~14)]，国内学会発表の抄録から調査したところ，10家系21例で，突然変異は，C30R, C30Y, T61I, C70S, C70G, C88Yの6か所であった．本邦のTRAPS患者の特徴は，欧米に多い腹痛，胸痛が少ないことである．これが，突然変異の場所との関連であるかは，症例を積み重ね，今後検討する必要がある．

以上の検索結果から，*TNFRSF1A*あるいは，*MEFV*に突然変異が証明される不明熱症例は，1割にも満たないことが判明した．臨床症状からは，TRAPSの可能性が高い症例もみられたが，多くは変異を証明できなかった．私たちは，*TNFRSF1A*あるいは，*MEFV*のhot spotの検索を行ったが，それ以外の部分の変異が存在した可能性，TRAPS症状をもつが*TNFRSF1A*遺伝子以外の異常の存在，TNFR1分子以外の分子の異常の存在，未知の自己炎症症候群である可能性，など考えられた．

TRAPSの病因・病態

TNFR1分子は，455個のアミノ酸からなり，アミノ酸29個のリーダーシークエンス，182個の細胞外ドメイン，21個の細胞膜貫通ドメイン，223個の細胞内ドメインからなる．細胞外ドメインには，4つのシステインリッチドメインが存在する．正常のTNFR1分子は，小胞体(endoplasmic reticulum；ER)からゴルジ体を通り，細胞表面へ発現される．3つのTNFR1分子は，TNFと結合する時に3量体を形成する．CRD1領域のpre-ligand assembly domain(PLAD)は，3量体を形成する前に，お互いに結合している．TNFと結合する場合，PLAD間の結合は解離し3量体を形成，TNFと結合する[15)]．したがって，このPLADの機能は，TNFからのシグナル伝達の窓口にあたる．TNFのシグナルによって，アポトーシス誘導，あるいは，サイトカイン産生に関連するNF-κBの活性化が誘導される．健常者の場合，3量体TNFR1分子は切断され，sTNFR1分子となる．それによって，TNFを中和するとともに，細胞内ではTNFからのシグナル伝達が結果的に抑制され，反応は終息する．このTNFR1分子に突然変異が存在する場合，以下に述べるようにTNFR1分子に変化がみられる．

現在まで，INFEVERS(遺伝性の発熱症候群などの突然変異の情報を掲示したサイト；http://fmf.igh.cnrs.fr/infevers/index.html)には，本症例を含め，88か所の遺伝子異常が登録されている(2008年11月30日現在)[16)]．90%以上が，切断部位が含まれるエキソン2, 3, 4, 6の部分の突然変異である．ほとんどがミスセンス変異であるが，スプライシング異常も報告されている[17)]．最近，TNFR1分子の切断部位の変異がある患者(V173D)が報告され，重症の心血管系疾患を合併していた[18)]．

1．これまでの病因論

(1)切断異常

TRAPSの病因として，TNFR1分子の切断(shedding)異常が考えられてきた[2)]．TNFR1分子の細胞外ドメイン(エキソン2, 3, 4の部分)に突然変異が存在した場合，切断酵素であるTNFα-converting enzyme(TACE)[19)]などのシェダーゼの働きが阻害され，TNFR1分子が細胞表面に留まり，TNFからの反応が持続する．そのため，発熱を含め，さまざまなTRAPSの症状が出現すると考えられた．このTNFR1分子の切断異常は，TRAPSの病態を説明する明快なメカニズムであったが，この異常だけで説明できないTRAPS患者は多い．遺伝子導入実験，TRAPS患者の細胞を使用した実験で，完全に切断異常を示した突然変異は，予想外に少数であった(C30S, P46L, T50M, T50K, C52F, F112I, I170Nなど)[4)]．さらに，TRAPS患者の細胞の種類によって，TNFR1分子の切断様式が異なっていた[20)21)]．

(2)アポトーシス異常

C43S突然変異のTRAPS患者から得られた皮膚線維芽細胞では，TNFによるNF-κBの活性化とアポトーシス誘導はともに低下していたが，サイトカイン産生能は保たれていた[21)]．アポトーシスは生体にとって必要な生命現象であり，この誘導低下は，本来生き残っては困る有害な細胞の長期生存を意味し，TRAPS患者の場合，TNFを含む炎症性サイトカインの持続産生と結びつく．最近，TRAPS患者(C43R, C55Y, C88Y, T50M)由来の好中球が，健常者に比べて，アポトーシ

ス刺激(cycloheximide＋TNF-α)に抵抗性であるという報告もあった[22].

(3)misfold & aggregate

突然変異が存在するTNFR1分子は，正常のTNFR1分子と比較して細胞質内にとどまっている割合が多く，結果的に細胞上の発現低下がみられるという報告がある[23]．前述したように，TNFR1分子は，細胞表面へ発現される前には，ゴルジ体に貯蔵されている[24]．TNFR1分子のCRD1領域に突然変異をもつ場合，ゴルジ体前後の蛋白の移動が抑制される[23]．遺伝子導入実験で，*TNFRSF1A*突然変異の多くが，TNFR1分子の発現が低下し，しかもTNFと結合しなかった[25]．つまり，TNFとは無関係であった．

C43S突然変異の遺伝子導入実験では，遺伝子導入だけでTNFに関係なく，NF-κBの活性化が生じた[26]．TRAPS患者の中でTNFの刺激と関係なく，潜在的にTNFR1分子が高発現，あるいは，TNFR1分子以下のシグナルが亢進している可能性があり，さらなる研究が行われた．ある突然変異が存在するTNFR1分子は，小胞体内，あるいはゴルジ体内に停滞し，一部が細胞質内に移動する．細胞質内のTNFR1分子は，ユビキチン化(ubiquitination)され，一部はプロテオゾームで分解される．残りのTNFR1分子は，うまくお互いが結合できず，凝集する(misfold & aggregate)[25][27]．その後TNFからのシグナルなしで，アポトーシス誘導，あるいは，サイトカイン産生に関連するNF-κBの活性化が誘導される[25]．この機序は，近年，関節リウマチ[28]，嚢胞性線維症，アルツハイマー病，パーキンソン病などの疾患の病因においても注目されている[29]~[31]．

(4)浸透度が低い突然変異の意義

TRAPSの病因の中で，「misfold & aggregate」と並び注目されているものが，R92Qを代表とする浸透度が低い突然変異を有するTRAPSである．これは，健常者にも多く存在する突然変異(陽性率1~5％)で，TRAPS症状が軽く，他の疾患の合併の報告が多い．最近では，多発性硬化症(multiple sclerosis)患者の中でTRAPS様症状を示す症例25例中6例(24％)にR92Q変異がみられたという報告があった[32]．さらに，R92Qは，動脈硬化の危険因子であるとの報告もある[33]．この突然変異が，合併する疾患の発症・進展に何らかの影響を与えている可能性が十分考えられる．R92Qの場合，症例報告が増えている．原因不明の急性腹膜炎症例で2回腹部手術を施行され，後にR92QとF60Vの変異が同時に存在(一人に2つの異なる突然変異が存在)していたことが判明した重症TRAPS症例もある[34]．R92Qの遺伝子導入実験では，突然変異のないTNFR1分子と比較して，発現，刺激後の切断様式，機能において，まったく差がなかった[27]．今後，浸透度が低いR92Qのような突然変異分子が，実際にどのような振る舞いをしているのか，どのような分子と会合してシグナルを伝達し，炎症を増悪させているのか，検討する必要がある．私たちが報告したT61Iも健常者の約3％に変異が存在し，R92Qと同様に浸透度が低い突然変異である．この変異が，TRAPS症状にどれだけ寄与しているか不明であるが，私たちが検索した不明熱症例で*TNFRSF1A*遺伝子変異が存在した4症例のうち，3例にT61I変異が存在したことから，何らかの因果関係はありそうである．

2．最近の病因論

前述したこれまでの病因論は，細胞への遺伝子導入研究に基づくものが主であった．しかし，導入する細胞の違いによって結果が異なり，実験システム自体に問題があることが指摘されるようになった．Nedjaiらは，TRAPS患者から得られた末梢血を利用して，異常を検討した[35]．彼らによれば，浸透度が高いC73R変異患者では，NF-κB p65活性が上昇しているが，浸透度が低いR92Q変異患者では，NF-κB p50活性が上昇していた．これらは，細胞刺激前から高く，*TNFRSF1A*遺伝子変異による異常と考えられた[35]．

NF-κB p65には，C末に転写活性化ドメインが存在するが，NF-κB p50には存在しない．NF-κB p50/p50ホモダイマーは，結果的に転写抑制へ働いている可能性がある．R92Q患者の細胞では，NF-κB p65が正常の2倍上昇(C73Rでは，約6.5倍)しているが，NF-κB p50/p50ホモダイマーのDNAへの結合が多いため，結果的にC73R患者ほどの活性化上昇が生じていないのではないかと彼らは結論づけた[35]．しかし，それらの潜在的なNF-κBの異常が，なぜ*TNFRSF1A*遺伝子変異に

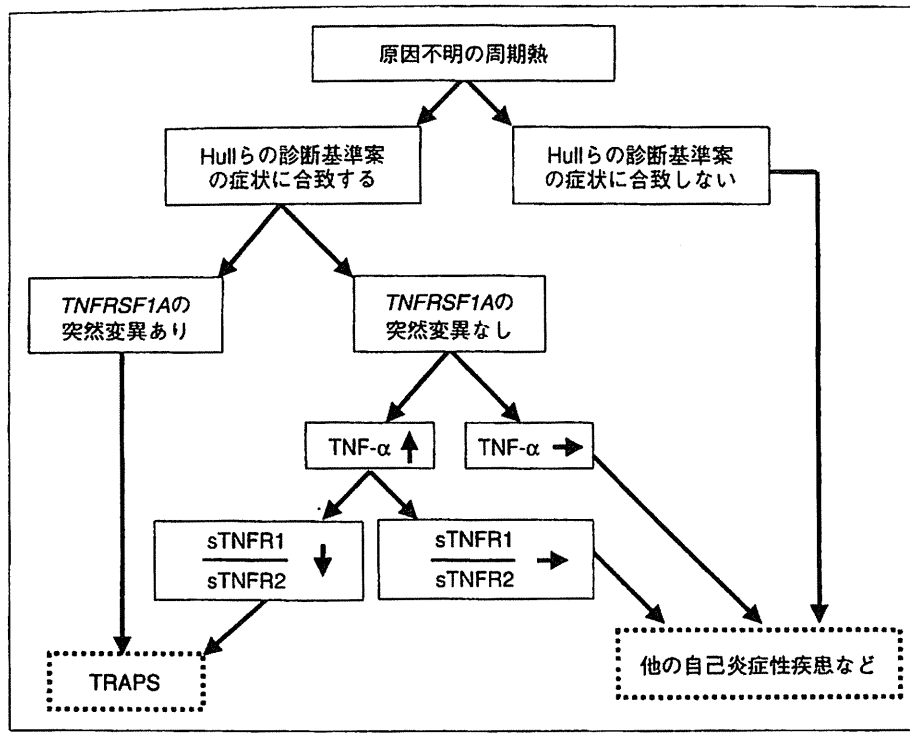

図1　TRAPS診断のためのフローチャート
Hullらの診断基準案[3]の臨床症状に，*TNFRSF1A*遺伝子の検索，および，血清中サイトカイン(TNF-α，sTNFR1, sTNFR2)を組み合わせて，TRAPS診断を試みた．

よって生じるかは，いまだに不明である．

TRAPSの診断基準

現在まで本邦における報告があったTRAPS患者は，Hullらの診断基準案[3]に照らし合わせてみると，欧米で頻度が多い胸痛，腹痛が少ない傾向があった．

TRAPSの病因が混沌としてきている現在，診断基準を作成することは，大変難しいことと思われる．前述のように私たちは，TRAPSの全国疫学調査を行い，これまでに多くの施設からTRAPS診断の相談を受けた．各患者の臨床症状，発熱時の血清サイトカイン測定，同意が得られた症例では遺伝子検索を行い，TRAPS診断を行った．その中で，突然変異がみられない孤発例の存在に気がついた．Hullらの診断基準案は，臨床症状を中心に作成されているが，臨床症状，検査データ，遺伝子情報を取り入れた多角的な診断基準が必要である．Touitouらは，診断基準があいまいな家族性地中海熱の診断で新しい時代にあった診断法を試みている[36]．私たちは，現在のTRAPS病因論，および，これまで経験したTRAPS症例での診断までのプロセスを再考し，TRAPS診断のためのフローチャートを作成した(図1)．

周期熱の原因として，感染症，悪性腫瘍，膠原病，炎症性肉芽腫疾患など，考えられる疾患を検索した上で，さらに診断がつかない場合，ここでは原因不明の周期熱とする．次に，Hullらの診断基準案の臨床症状(表1の大項目1～3)に当てはめ，合致しない場合，TRAPSは考えにくく，他の自己炎症性疾患を検討する．合致する場合，*TNFRSF1A*遺伝子検索を行う．*TNFRSF1A*遺伝子に突然変異が存在すれば，TRAPSと診断する．突然変異が存在しない場合，検査データを活用する必要がある．血清中のTNF-αが上昇し，かつ，sTNFR1分子がsTNFR2分子に比較して低値を示す場合，何らかのTNFR1分子の機能異常を呈していると考えられ，TRAPSと診断する．家族歴のない孤発例は，これに当てはまる．一

方，血清中のTNF-α上昇に相関して，sTNFR1分子が上昇している場合，TNFR1分子の機能は正常と考えられ，他の自己炎症性疾患(家族性地中海熱など)を検討する．血清中のTNF-αが上昇していない場合，*TNFRSF1A*遺伝子の突然変異も存在していないならば，たとえばTNFR1分子の細胞質内凝集も起こる可能性はなく，TRAPSは考えにくい．他の自己炎症性疾患，あるいは，さらなる不明熱の鑑別(感染症，悪性腫瘍，膠原病，炎症性肉芽腫疾患など)を検討する．以上，現在まで解明されているTRAPS病因論から検討した診断までのプロセスを示した．

TRAPSの治療法

TRAPS患者の治療は，コルヒチンの有効率は低く，ステロイド剤中心である[4]．この点が家族性地中海熱と大きく異なる．ステロイド剤によって，多くのTRAPS患者の症状は軽減できたが，発熱を含めた発作の回数は減らせていない．最近，TNFを中和する生物学的製剤が，RA患者やクローン病患者に使用され，絶大なる効果が報告されている．TRAPS患者にもetanercept(TNFR2融合蛋白)が使用され，発作の回数の減少とステロイド剤の減量ができたとの報告がある[18][37]~[39]．しかし，病因に関係するのかもしれないが，etanerceptがまったく効かない症例，また，同じ生物学的製剤のinfliximabでは，症状の悪化がみられた症例も存在する[40]．私たちは，サイトカイン産生抑制効果がみられる免疫抑制剤のtacrolimus(FK506)をTRAPS患者に使用したところ，血清中のTNF-α値の低下と筋膜炎の軽減を認めた[41]．これまでステロイド増量によって，発熱の軽減，炎症反応の低下はみられたが，血清中のTNF-α値は高値が持続していた．しかし，tacrolimus投与によって，血清中のTNF-α値はすみやかに低下した．同時に，MRI上筋膜炎の軽減を認めたことから，TNF-αを産生していると想像される筋膜浸潤CD68陽性細胞へのtacrolimusの作用が示唆された．近年，IL-1を中和する生物学的製剤(anakinra)が，TNF関連の生物学的製剤無効のTRAPS症例に有効であるとの報告もある[42]．

おわりに

本邦では，*TNFRSF1A*遺伝子に突然変異をもつTRAPS(TNF receptor-associated periodic syndrome)症例は10家系21名と少ない．私たちのこれまでのTRAPS全国調査でも，ほとんどの症例は，*TNFRSF1A*遺伝子に突然変異のない孤発例であった．前述したが私たちの検索結果では，*TNFRSF1A*あるいは，*MEFV*に突然変異が証明された不明熱症例は，1割にも満たなかった．他の部位の変異，*TNFRSF1A*遺伝子以外の異常の存在，TNFR1分子以外の分子の異常の存在，未知の自己炎症症候群である可能性，など考えられるが，一例一例詳細に検討する必要があるであろう．その結果，TRAPSの病因解明にとどまらず，まだ不明な慢性炎症疾患のメカニズムにも迫れるものと期待している．

追記：この原稿をお読みになった先生方やお知り合いの先生で，TRAPSの可能性がある不明熱・周期熱患者(原因不明の38.3℃以上の発熱が3週間以上持続し周期的に出現する)をおもちの方，また，診断基準に関してご意見がある方は，ご遠慮なくidah@net.nagasaki-u.ac.jpまでご連絡ください．

全国の有志の先生方と2008年7月に全国規模で「自己炎症疾患研究会」を立ち上げました．本邦症例の蓄積，ガイドライン作成など行っていく予定です．ご賛同いただける方はご連絡ください．

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