Familial Mediterranean fever: overview of pathogenesis, clinical features and management

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\textbf{ABSTRACT}
Familial Mediterranean fever (FMF) is the most common monogenic autoimmune disease, and is characterized by recurrent attacks of fever and polyserositis. It is associated with mutations in the \textit{MEFV} gene encoding pyrin, which result in inflammasome activation and the uncontrolled production of IL-1\textbeta. FMF mainly affects individuals originating from the Mediterranean basin; however, a Japanese nationwide survey demonstrated that FMF is not uncommon in Japan. The survey also indicated that Japanese FMF patients are clinically or genetically distinct from Mediterranean FMF patients, suggesting a genotype–phenotype correlation. In Japanese patients with FMF, \textit{MEFV} exon 10 mutations are associated with the more typical FMF phenotype. Conversely, Japanese FMF patients with mutations in \textit{MEFV} exons 2 or 3 present with an atypical FMF phenotype. Colchicine is the mainstay of FMF treatment, and its regular use prevents febrile attacks and decreases the long-term risk of AA amyloidosis. However, a minority of FMF patients are colchicine-resistant, and anti-IL-1 treatment has proven beneficial in suppressing inflammation in these patients. Although Japanese FMF patients may develop less severe disease compared with Mediterranean FMF patients, they should nevertheless be treated early to prevent recurrent attacks and the subsequent development of AA amyloidosis.

\section{1. Introduction}
Autoinflammatory diseases are defined by recurrent episodes of generalized inflammation and fever in the absence of infections or autoimmune causes [1]. Hereditary autoinflammatory diseases are genetically determined multisystem disorders caused by dysfunctions in innate immunity [2]. Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease [3]. It is an ethnically restricted disease, which predominantly affects people of Mediterranean descent including Armenians, Turks, Arabs, and Jews [4]. However, patients with FMF have also been reported in European countries and East Asia [5]. Additionally, a high prevalence of FMF (31.9\%) was reported in Japanese patients with unexplained fever [6].

Familial Mediterranean fever is characterized by recurrent, self-limited fever associated with polyserositis or synovitis [7]. The \textit{MEFV} gene (\textit{MEFV}) was identified as causative of FMF by two distinct consortia in 1997 [8,9]. \textit{MEFV} encodes pyrin, which forms an element of the NLRP3 inflammasome complex that modulates production of the pro-inflammatory cytokine interleukin-1\textbeta (IL-1\textbeta); FMF may therefore be classified as an inflammasomopathy [10]. In this review, we describe recent knowledge of FMF basic and clinical evidence.

\section{2. Pathogenesis}
IL-1\textbeta plays a major role in the pathogenesis of FMF, and it is likely that FMF mutations increase IL-1\textbeta production [3]. However, it had been unclear whether causative \textit{MEFV} mutations were loss-of-function or gain-of-function types. Supporting the loss-of-function model, Papin et al. [1] demonstrated an increase in caspase-1 activation and IL-1\textbeta secretion as a result of pyrin knockdown. On the other hand, supporting the hypothesis of a gain-of-function model, Chae et al. [12] demonstrated that knock-in mice with FMF-associated B30.2 mutations (\textit{MEFV} exon 10 mutations), but not pyrin-deficient mice, showed a severe spontaneous inflammatory phenotype. This point remains controversial. Recent studies have shown that pyrin recognizes bacterial modifications in Rho GTPases, which results in...
inflammasome activation and increases in IL-1β. Pyrin does not directly recognize Rho modifications, but probably associates with a Rho effector kinase, which is a downstream molecule in the actin cytoskeleton pathway [13].

3. Genetics

*MEFV* is located on chromosome 16, and is composed of 10 exons. In 1997, *MEFV* mutations were found to be associated with FMF susceptibility. To date, more than 300 *MEFV* sequence variants have been reported [14]. In 2012, a consensus was reached to test 14 *MEFV* variants, including nine that are pathogenic (M694V, M694I, M680I, V726A, R761H, A744S, I692del, E167D, and T267I) and five of unknown significance (E148Q, K695R, P369S, E479L, and I591T) [15].

A Japanese nationwide survey of FMF found that 86.5% of Japanese FMF patients had one or more *MEFV* mutations or polymorphisms. Japanese FMF patients have only two *MEFV* exon 10 variants: M694I and M680I [16]. The most frequent genotype was found to be M694I/E148Q (19.8%), followed by M694I/normal (12.7%), whereas the M694I/M644I genotype was only observed at a frequency of 6.3%. Allelic frequencies of *MEFV* variants were: M694I (29.4%), E148Q (31.3%), L110P (11.5%), P369S (5.6%), and R408Q (5.6%). Japanese FMF patients reported mild or incomplete forms of the FMF phenotype. Several factors, including *MEFV* genotype, are thought to contribute to the phenotype variability of FMF. We investigated genotype–phenotype correlations in Japanese patients with FMF, and found that patients with a typical FMF phenotype had a shorter duration of febrile attacks, experienced pleuritis and peritonitis, and harboured *MEFV* exon 10 mutations [17]. Conversely, patients with atypical FMF phenotypes had a lower frequency of febrile episodes, presented with arthritis and myalgia, and had mutations in *MEFV* exons 2 or 3. As shown in Figure 1, typical FMF phenotype frequencies were decreased in patients carrying low-penetrance mutations (those in exons 2 and 3), while the opposite trend was seen for the atypical FMF phenotype. Conversely, *MEFV* exon 10 mutations were associated with the more typical FMF phenotype.

Several studies have demonstrated associations of *MEFV* mutations with different inflammatory disorders, such as Behçet’s disease [18] and Sweet’s syndrome [19]. The report of a growing number of similar cases associated with *MEFV* suggests that pyrin is a key regulatory element of innate immunity that affects inflammatory processes in these diseases [20–22].

4. Epigenetics

Familial Mediterranean fever patients without *MEFV* mutations were isolated in a nationwide survey of Japanese FMF patients [16]. FMF patients with similar *MEFV* genotypes may present with heterogeneous clinical manifestations because of the influence of other modifier genes [23], epigenetics, and environmental factors [24]. Thus, epigenetic mechanisms such as histone modifications, methylation, and microRNAs (miRNAs) may play a role in the pathogenesis of FMF [25]. miRNAs are small, non-coding RNAs that regulate gene expression at the post-transcriptional level by degrading mRNA or blocking its transcription [26]. Their circulating levels have previously been described in rheumatic disease, but have not yet been elucidated in FMF, although they might affect disease pathogenesis. Circulating miRNAs in FMF have been investigated between febrile attack periods and afebrile seizures to identify potential FMF biomarkers and to clarify their gene targets. Koga et al. [27] found that miR-204-3p was greatly decreased in the serum of FMF patients during a febrile attack (Figure 2). Bioinformatic analysis predicted that miR-204-3p targets genes implicated in the TLR pathway such as IL-6 and IL-12p40 through the regulation of PI3Kγ signalling. These findings indicate that miR-204-3p could be a useful biomarker in FMF patients, and serve as a suppressor of inflammatory cytokines in FMF by targeting the PI3Kγ pathway [27].

Because pyrin is a component of NLRP3, which is a pathogen recognition receptor, it is conceivable that microorganisms affect FMF pathogenesis. Khachatryan et al. [28] reported that the
composition and divergence of microbiota differed during attack and attack-free periods as well as between FMF patients and healthy controls. Although FMF is a monogenic disorder, epigenetic factors and microbiota may influence FMF disease or phenotypic expression. Further studies on the effect of epigenetics, microbiota, and the environment on FMF are needed to elucidate FMF pathogenesis.

5. Clinical manifestations of Japanese FMF patients

Familial Mediterranean fever manifests as recurrent attacks of serosal inflammation (peritonitis or pleuritis) or synovitis, which are accompanied by fever and resolve spontaneously. Disease onset usually occurs during childhood or adolescence [16], but the initial symptoms of Japanese FMF patients develop later in life (mean disease onset, 19.1 ± 2.1 years). This age of onset differs significantly from Mediterranean patients who develop FMF before the age of 20 in 90% of cases. The late onset of disease and the mild FMF phenotype of Japanese patients may be associated with the MEFV genotype, which is characterized by an absence of the M694V genotype and lower frequencies of MEFV exon 10 mutations or homozygotes. Typical manifestations of FMF include fever, peritonitis, pleuritis, and arthritis. The prevalence of febrile attack (95.5%), chest pain (pleuritic, 35%), and arthritis (31.3%) were comparable between Japanese and Mediterranean FMF patients, while abdominal pain (peritonitis, 62.7%) and AA amyloidosis (3.7%) were less prevalent among Japanese FMF patients (Table 1) [29–31]. The most common neurological manifestations in FMF are headache and myalgia. Aseptic meningitis [32] also has been described in Japanese patients with FMF. Myalgia particularly affects the legs, and protracted febrile myalgia is considered to be one of the muscular manifestations of FMF [33]. It can be resolved with prednisolone treatment.

Erysipelas-like erythema is one of the specific uncommon skin manifestations of FMF. It is associated with skin lesions that usually appear on the legs, and are red, hot, swollen, sharply bordered, and painful eruptions.

6. Diagnosis of FMF

Although various MEFV variants have been identified in association with FMF, the disease should be diagnosed from clinical manifestations. Short-lived (1–4 days) febrile episodes accompanied by serositis (pleuritic and peritonitis) and synovitis that respond to colchicine treatment are required for a diagnosis.
However, various diagnostic criteria have been proposed for different populations. In the diagnosis of Japanese patients with FMF, modified Tel–Hashmer criteria (Table 2) were suggested by our study group to be used as simplified diagnostic criteria [16]. These include: recurrent febrile episodes (three or more episodes lasting 12 h to 3 days with a fever of ≥38°C), and eight minor criteria (a febrile attack with one of the accompanying seven symptoms including abdominal pain from peritonitis; chest pain from pleuritis; monoarthritis; pericarditis; scrotal pain from orchitis; headache from aseptic meningitis; or a favourable response to colchicine treatment). A diagnosis of FMF was determined if the patient exhibited the major criteria and one or more minor criteria. Differential diagnoses include infections, malignancy, and autoinflammatory diseases.

Table 2. Diagnostic criteria for FMF.

| Major criteria |
|----------------|
| Recurrent febrile episodes as 3 or more episodes lasting 12 h to 3 days with fever of 38°C or more |

| Minor criteria |
|----------------|
| Abdominal pain due to peritonitis |
| Chest pain due to pleuritic |
| Pericarditis |
| Monoarthritis of hip, knee or ankle |
| Fever alone |
| Scrotal pain due to orchitis |
| Headache due to aseptic meningitis |
| Favourable response to colchicine |

A diagnosis of FMF is reached if the patient has 1 major criteria plus 1 or more minor criteria.

7. Complications

Secondary amyloidosis is the most serious complication of FMF. Many studies have focused on the risk factors affecting the development of amyloidosis, such as the MEFV genotype, and SAA1 polymorphisms [35]. Colchicine treatment prevents the development of amyloidosis, but some patients are refractory to colchicine. In these cases, biologic treatments have been suggested to prevent the development of AA amyloidosis.

8. Biomarkers for FMF

Little information is available about biomarkers of autoinflammatory disorders, especially FMF. S100A12, a product of activated neutrophils, has been reported to be a sensitive biomarker for FMF. Kallinich et al. [36] demonstrated that neutrophils from M694V-positive patients secreted more S100A12, IL-18, and caspase-1 compared with neutrophils from healthy controls. As shown in Figure 3, circulating levels of cleaved IL-1β (active form, p17), which is induced during inflammasome activation, were significantly higher in patients with FMF and were particularly elevated during febrile attacks [37]. The cleaved form of IL-1β therefore appears to be a biomarker for monitoring disease activity. CD64 (FcγR1) expression in polymorphonuclear neutrophils was also increased in FMF patients compared with those with autoimmune diseases [38]. Koga et al. [39] identified...
Familial Mediterranean fever is not restricted to Mediterranean countries, and a lack of awareness of this autoinflammatory disease elsewhere in the world, including Japan, may lead to a delay in its diagnosis. This can cause the development of the life-threatening complication AA amyloidosis. FMF is not uncommon in Japan, and the mild phenotype of Japanese FMF patients may reflect their MEFV genotype. We hope that this review will raise physician awareness of this disease, enabling patients to obtain an early diagnosis and precise treatment.

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**9. Treatment**

Colchicine remains the mainstream treatment for patients with FMF, and has been shown to prevent the complication of secondary amyloidosis [40]. It is well-tolerated, even in paediatric FMF patients, with gastrointestinal side effects being the most common, including vomiting, diarrhoea, and the transient elevation of transaminases. The optimal dosage of colchicine varies according to different clinical practice, but it is started at a dose of 0.5 mg/day in most adult patients, and adjusted according to disease activity and tolerance in follow-up. The dose can also be reduced to decrease side effects [41]. Frequencies of febrile attack and the presence of subclinical inflammation are indications to increase the colchicine dose. A favourable therapeutic effect was seen in 91.8% of Japanese FMF patients treated with colchicine, and the mean dose required to control symptoms was 0.89 ± 0.45 mg/day [16]. The maximum dose given to adults in Western countries is 2–3 mg/day [41]. However, more than 15% of FMF patients are non-responders to colchicine treatment, or do not tolerate the drug mainly because of gastrointestinal symptoms. Therefore, in recent years, biologics have been used to treat such patients. Because the mutated pyrin protein plays an important role in the regulation of IL-1β activation, anti-IL-1 treatment has proven beneficial in improving clinical manifestations in FMF patients who are resistant or intolerant to colchicine [42].

Canakinumab is a human IgG1 monoclonal antibody directed against IL-1β. Canakinumab binds human IL-1β and neutralizes its biological functions, and demonstrates specificity because it does not bind either IL-1α or IL-Ra [43]. The efficacy and safety of Canakinumab for the treatment of TRAPS, HIDS/MKD and FMF were evaluated in phase III study (N2301) consisting of three separate disease cohorts [44]. In the primary efficacy endpoint (the proportion of responders), Canakinumab was shown to be superior to placebo for three disease cohorts. Canakinumab became the approved therapy for colchicine-resistant FMF in Japan, which highlights its importance as the alternative treatment in FMF. It has a half-life of 21–28 days, so can be administered every eight weeks. The recommended dose is 150 mg for adults, and 2 mg/kg subcutaneously for children.

IL-6 induces inflammatory responses as well as an increase in acute phase reactants, such as CRP and SAA. Tocilizumab (TCZ) is a humanized, anti-human IL-6 receptor monoclonal antibody that blocks soluble and membrane-bound gp130, an IL-6 receptor. We reported increased IL-6 levels during FMF febrile attacks [39]. In accordance with these findings, a Japanese colchicine-resistant FMF patient who was successfully treated with TCZ was reported [45]. Subsequently, Yilmaz et al. [46] reported 11 patients with AA amyloidosis secondary to FMF who were successfully treated with TCZ. These findings suggest that TCZ should be recommended for patients with FMF complicated with AA amyloidosis during early stages of disease, and those who are refractory to colchicine to prevent the development of AA amyloidosis.

**10. Conclusions**

Canakinumab binds human IL-1β and neutralizes its biological functions, and demonstrates specificity because it does not bind either IL-1α or IL-Ra. The efficacy and safety of Canakinumab for the treatment of TRAPS, HIDS/MKD and FMF were evaluated in phase III study (N2301) consisting of three separate disease cohorts. In the primary efficacy endpoint (the proportion of responders), Canakinumab was shown to be superior to placebo for three disease cohorts. Canakinumab became the approved therapy for colchicine-resistant FMF in Japan, which highlights its importance as the alternative treatment in FMF. It has a half-life of 21–28 days, so can be administered every eight weeks. The recommended dose is 150 mg for adults, and 2 mg/kg subcutaneously for children.
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