Variant FMF識別する分類基準

① 発熱期間が4日以内
② 1ヶ月の発作回数が1回以上
③ 家族歴あり
④ exon10に変異を認める
⑤ exon3に変異を認めない

（各1点）

3点以上　Typical（73.7%）＝特異度
2点以下　Variant（83.0%）＝感度

家族性地中海熱　二次調査票

厚生労働科学研究費補助金　難治性疾患等克服研究事業
（難治性疾患克服研究事業）
「家族性地中海熱の病態解明と治療指針の確立」班

□典型例　　□非定型例（どちらか一方にチェックをいれてください）

この調査票は実態把握のためのみに使用し、個人情報は目的以外には利用致しません。
以下の問いについて、当てはまる方に✓をお付け下さい。また、下線部に数値等をご記入下さい。

貴施設名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿　記載者氏名：＿＿＿＿＿＿＿＿＿＿＿＿ 記載年月日：平成 24 年＿＿＿＿月＿＿＿＿日　E-mail：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿ 住所：〒　電話：＿＿＿＿＿＿＿＿　FAX：＿＿＿＿＿＿＿＿	
調査対象者番号（調査のために用いる ID 番号があればご記入下さい。カルテ番号は記入しないで下さい）：＿＿＿＿＿＿＿＿ 生年月日：明・大・昭・平＿＿＿＿年＿＿＿＿月＿＿＿＿日　性別：□男　□女　年齢：＿＿＿＿歳	
診断の確実度　□確定診断例　□疑い例 発症年齢（推定）＿＿＿＿＿（　　）歳　診断時年齢＿＿＿＿＿＿＿＿歳	
家族歴内発症	□あり（続柄:□父　□母　□兄　□弟　□姉　□妹　□その他）　□なし□不明 血族結婚の有無：□あり　□なし　□不明
臨床症状	周期性発熱　□あり　1 回の発熱続期間（　　）最高体温（　　℃） □　なし　□不明 発作の頻度：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿　[例：2-3 ヶ月に 1 回　など] 月経との関連：□あり（月経中に□軽減　□増悪）　□なし　□不明
	腹痛発作　□あり（□全般性　□限局性）　□なし　□不明 胸痛発作　□あり（□全般性　□限局性）　□なし　□不明 関節炎発作　□あり（部位：　　）　□なし　□不明 心膜炎発作　□あり　□なし　□不明 皮疹　□あり　（□丹毒様紅斑　□その他の発疹）　□なし　□不明 筋痛　□あり　□なし　□不明　　頭痛　□あり　□なし　□不明 その他の症状（　　） 二次性アミロイドーシス　□あり（臓器　　）□なし　□不明

<table>
<tr><td>検査所見</td><td>検査値（発作時）：WBC　　CRP
SAA　　ESR　　IgD
検査値（非発作時）：WBC　　CRP
SAA　　ESR　　IgD</td></tr>
<tr><td>併存症・既往歴の有無</td><td>合併疾患　□あり
□　自己免疫疾患　（病名　　）
□　その他　（病名　　）
□なし　□不明</td></tr>
<tr><td>治療</td><td>コルヒチンの投与　□あり　□なし（1日の投与量：　　mg/day）□不明
コルヒチンに対する反応性　□有効　□無効　□副作用のため中止　□不明
その他の薬剤（薬剤名：　　投与量：　　）
□有効　□無効　□不明</td></tr>
<tr><td rowspan="2">遺伝子診断</td><td>□施行あり　□施行なし　□不明
（施行時年齢：　　歳　　ヶ月）</td><td>未施行の場合：
遺伝子診断を希望なさいますか。
□希望する□希望しない□わからない</td></tr>
<tr><td colspan="2">（施行した場合）結果：</td></tr>
<tr><td rowspan="2">現在の状況
（診断時の比較）</td><td>□治癒　□改善　□不変　□悪化　□死亡</td><td>最終受診日　平成　　年　　月　　日</td></tr>
<tr><td colspan="2">（死亡の場合）死亡年月日：平成　　年　　月　　日　死因：（　　）
剖検：　□あり　□なし　□不明</td></tr>
<tr><td rowspan="3">症例報告の有無</td><td colspan="2">学会発表：□あり　□なし　□不明</td></tr>
<tr><td colspan="2">（学会発表がある場合）学会名：＿＿＿＿＿＿＿＿＿＿
第（　　）回　（　　）年</td></tr>
<tr><td colspan="2">紙上発表：□あり　□なし　□不明
雑誌名：＿＿＿＿＿＿＿＿（　　）年（　　）巻（　　～　　）頁</td></tr>
</table>

ご協力ありがとうございました。

ホームページアドレス

http://www.nmc-research.jp/fmf/index.html

Familial Mediterranean Fever (FMF)
家族性地中海熱

厚生労働科学研究費補助金
難治性疾患克服研究事業
「家族性地中海熱の病態解明と治療指針の確立」研究班

取り組んでいます

- HOME
- 班員名簿
- 家族性地中海熱とは
- FMF診療ガイドライン（暫定版）

更新情報

2011年12月7日
・家族性地中海熱(FMF)の診療ガイドラインを掲載しました。

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II. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

＜蔵書＞

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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川上　純，右田清志，井田弘明.	自己炎症疾患. 特集　免疫反応と疾患. 自己炎症疾患・炎症性疾患の免疫異常.	medicina.	50(3)	458-462	2013

III. 研究成果の刊行物・別刷

17. 自己炎症疾患

autoinflammatory disorders

長崎医療センターリウマチ科　右田清志・宮下賜一郎

診断の要点	●遺伝性自己炎症疾患は，幼小児期より繰り返される発熱を伴っていることが多いが，特徴的な皮疹，関節炎など，各疾患に特徴的な全身の炎症に起因する臨床所見を伴っており，臨床像の把握が診断に重要である． ●また各疾患の責任遺伝子が同定されており，遺伝子診断が診断の補助となる．
治療の要点	●各疾患に特異的治療法があり，それに準じた治療が必要である． ●原因不明のまま放置されると，二次性アミロイドーシスなど重篤な臓器障害を併発するので，早期治療介入が必要である． ●近年の抗サイトカイン療法の進歩により，CAPS に対する IL-1 阻害療法，TRAPS に対する可溶型 TNF レセプターなど，新規治療薬が登場し，これまで難病と考えられた遺伝性自己炎症疾患の治療が大きく変貌している．

歴史と定義

自己炎症疾患という概念は，TNF 受容体関連周期熱症候群（TRAPS）の原因遺伝子として TNF receptor superfamily 1A（TNFRSF1A）を同定した Kastner らによって提唱された[1]．

自己炎症疾患は周期熱で象徴される繰り返す炎症が特徴であり，自己免疫疾患，感染症と異なり，自己抗体，自己反応性 T 細胞，および病原体は同定されない．病因としては，獲得免疫ではなく，自然免疫系の異常が考えられる．遺伝性自己炎症疾患の特徴は，遺伝子の変異により生じる自然免疫系の活性化により，周期熱，皮膚結合織の炎症が起こると同時に IL-1β，TNF-α などのサイトカインシグナルの活性化が起こっていることが示されている[2]．したがって，IL-1，TNF 等に対する抗サイトカイン療法の有効性が注目されている．

従来の自己炎症疾患は，TRAPS，家族性地中海熱（familial mediterranean fever：FMF），cryopyrin 関連周期熱症候群（cryopyrin-associated periodic syndrome：CAPS）（家族性寒冷自己炎症症候群（FCAS），Muckle-Wells 症候群（MWS），CINCA 症候群の 3 疾患）など，周期性発熱を呈する遺伝性免疫疾患が対象とされていたが，現在，自己炎症の概念は拡大しており，遺伝子異常はあるものの周期熱を欠く疾患，さらには遺伝子異常はなく従来リウマチ性疾患と考えられていた痛風，Behçet 病，成人発症 Still 病，全身型 JIA（juvenile idiopathic arthritis）も広義の自己炎症疾患と考えられるようになっている．

臨床の実際

1．臨床像からみた分類

自己炎症疾患の概念の拡がりに伴い，その分類に関してさまざまな意見があるが，臨床所見による分類を Table 1[3] に示す．

自己炎症疾患は，遺伝性周期熱症候群（hereditary recurrent fevers），突発性発熱疾患（idiopathic febrile syndromes），化膿性疾患（pyogenic disorders），内芽腫性疾患（granulomatous diseases），皮膚・骨組織の自己炎症疾患（autoinflammatory disorders of skin and bone），代謝性疾患（metabolic disorders），補体の異常に伴う疾患（complement disorders），血管炎（vasculitis），マクロファージ活性化症候群（macrophage activation syndromes）に大きく分類される．

狭義の自己炎症疾患と考えられている遺伝性の周期熱症候群は，その発症機構からインフラマゾームの機能異常に起因する IL-1β 産生亢進が原因である FMF，CAPS，および受容体蛋白のミスホールディングにより発症する TRAPS が代表的

Table 1. 自己炎症疾患の臨床分類

疾患名	責任遺伝子	発症機構
hereditary recurrent fevers		
familial mediterranean fever(FMF)	*MEFV(pyrin)*	インフラマゾームの活性化
TNF receptor-associated periodic syndrome (TRAPS)	*TNFRSF1A(TNFR1)*	蛋白のミスホールディング
hyperimmunoglobulinemia D syndrome (HIDS)	*MVK(mevalonate kinase)*	インフラマゾームの活性化
familial cold autoinflammatory syndrome (FCAS)	*NLRP3/CIAS1(NLRP3/cryopyrin)*	インフラマゾームの異常
Muckle-Wells syndrome(MWS)	*NLRP3/CIAS1(NLRP3/cryopyrin)*	インフラマゾームの異常
chronic infantile neurological cutaneous articular syndrome(CINCA)	*NLRP3/CIAS1(NLRP3/cryopyrin)*	インフラマゾームの異常
idiopathic febrile syndromes		
systemic onset juvenile idiopathic arthritis (SoJIA)	(−)	不明
adult-onset Still's disease	(−)	不明
pyogenic disorders		
pyogenic arthritis with pyoderma gangrenosum and acne(PAPA)	*PSTPIP1/CD2BP1(PSTPIP1/CD2BP)*	PSTPIPI と pyrin の結合による IL-1β の活性化
granulomatous diseases		
chronic granulomatous synovitis with uveitis and cranial neuropathy(Blau syndrome)	*NOD2/CARD15(NOD2/CARD15)*	NF-κB の活性化
Crohn's disease	(−)(*NOD2, ATG16L1, IRGM*)?	NF-κB の活性化
autoinflammatory disorders of skin and bone		
deficiency in IL-1 receptor antagonist (DIRA)	*IL1RN(IL-1Ra)*	IL-1RN の欠損
Majeed syndrome	*LPIN2(Lipin-2)*	不明
chronic recurrent multifocal osteomyelitis (CRMO)	(−)	不明
synovitis acne pustulosis hyperostosis osteitis(SAPHO)	(−)	不明
metabolic disorders		
gout(monosodium urate deposition)	(−)(*SLC2A9/GLUT9, ABCG2*)?	結晶によるインフラマゾームの活性化
pseudogout (calcium pyrophosphate dihydrate deposition)	(−)	結晶によるインフラマゾームの活性化
complement disorders		
atypical hemolytic-uremic syndrome(aHUS)	*CFH(complement factor H), MCP(CD46), CFI(complement factor I), CFB(complement factor B)*	C3b の機能異常
vasculitis		
Behçet's disease	(−)	不明
macrophage activation syndromes		
familial hemophagocytic lymphohistiocytosis (HLH)	*UNC13D(Munc13-4), PRF1(perforin 1), STX11(syntaxin 11)*	細胞障害性 T 細胞の機能低下による代償性のマクロファージ活性化

[文献 3)より引用，改変]

な疾患である．IL-1 受容体アンタゴニスト欠損症候群(DIRA)や，幼小児期から始まる凍瘡様皮疹と弛張熱，結節性紅斑様皮疹，指趾の拘縮，限局性脂肪筋肉の萎縮を特徴とし，最近，免疫プロテオゾームをコードする遺伝子が責任遺伝子として同定された中條-西村症候群[4]も，遺伝性自己炎症疾患に属する．また代謝性疾患である痛風，偽痛風は，尿酸結晶等がインフラマゾームを活性化することより自己炎症疾患と考えられている．

2．臨床症状と治療

遺伝性周期熱症候群を中心に，その臨床像，治療に関して解説する[5]．インフラマゾームの機能異常に起用する IL-1 産生過剰産生が原因と考えられる疾患としては，CAPS と FMF，高 IgD 症候群(HIDS)があげられる．

CAPS は NLRP3 の遺伝子異常によりインフラマゾームの活性化，IL-1β の過剰産生により発症する．CAPS は症状の重症度順に，FCAS，MWS，CINCA 症候群の 3 つの症候群からなり，症状としては，寒冷蕁麻疹，発熱，重症型では，難聴，関節拘縮，二次性アミロイドーシスをきたし，FCAS，MWS，CINCA 症候群の順に重症度が増す．CAPS 全体での診断基準は存在せず，個々の症候群について，特徴的臨床症状の有無による臨床的診断基準が提唱されている．NLRP3 の遺伝子変異が診断の補助となるが，遺伝子変異型と表現型が必ずしも一対一に対応していない特徴がある．また CINCA 症候群では，NLRP3 モザイクによる発症機構が示されており，通常のシークエンスでは遺伝子変異を検出できない可能性がある．

CAPS の病態は IL-1 の過剰産生であり，IL-1 阻害薬が著効する．現在 anakinra，canakinumab 等の生物学的製剤が臨床応用されている．

FMF は，NLRP3 インフラマゾームの制御蛋白である Pyrin をコードする *MEFV* 遺伝子変異で発症する．遺伝形式は常染色体劣性であるが，本邦例では孤発例，ヘテロ変異で発症するケースが少なくない．症状は，周期性発熱に加え，漿膜炎，滑膜炎(関節炎)を伴っていることが特徴である．治療に関しては，80% 以上の症例で colchicine が有効であるが，無効性に対しては IL-1 阻害薬の有効性が報告されている．

HIDS は，乳児期からみられる周期性発熱に伴って出現する皮疹，腹部症状，大関節を中心とした関節炎を特徴とする．血清の IgD の上昇は必ずしも伴ってないこともあり，発熱時の尿中メバロン酸の上昇が診断に有用である．メバロン酸経路の下流の代謝産物であるグラニルグラニルピロリン酸の不足が，IL-1β の分泌亢進につながっていることが示されている．

TRAPS は，1 型 TNF 受容体(TRAPS1)をコードする *TNFRSFIA* 遺伝子で起こる常染色体優性の自己炎症疾患である．変異型 TNFRI は，その構造異常から下流のシグナル亢進により自己炎症が誘導されると考えられている．周期性発熱に加え，皮疹，筋痛，腹痛，結膜炎などの症状を伴う．治療としては，副腎皮質ステロイド薬と可溶型 TNF 受容体である etanercept が有効である．

NF-κB の活性化が原因と考えられている自己炎症疾患として，若年発症サルコイドーシス/Blau 症候群があげられる．ともに NOD 様受容体(NLR)ファミリーに属する NOD2 の遺伝子変異により，最終的に NF-κB が活性化され発症すると考えられている．症状としては結節性紅斑，ブドウ膜炎，特徴的な関節炎(嚢腫状の腫脹，拘縮を伴う)があげられる．

おわりに

自己炎症疾患は，まだ十分認知されているとはいえず，不明熱，原因不明の関節炎として見逃されているケースも少なくないと思われる．また無治療で経過すると，再発する炎症で二次性アミロイドーシスなど不可逆性の臓器合併症を併発するリスクもある．これら自己炎症疾患の一部には，特異的な治療法も存在することを念頭に置き，特異的な症状から臨床診断を行い，場合によっては遺伝子診断を組み合わせることで早期発見，早期治療介入に努めることが肝要である．

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tis also may experience long-lasting remission after a single canakinumab injection. This would make IL-1 inhibition even more appealing as a potential treatment of recurrent idiopathic pericarditis.

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Interleukin-1β suppression in Blau syndrome: comment on the article by Martin et al

To the Editor:

We read with great interest the recent article by Martin et al on the role of interleukin-1β (IL-1β) secretion in Blau syndrome (1). To evaluate synergistic effects, the authors measured IL-1β secretion levels in peripheral blood mononuclear cells (PBMCs) isolated from 5 patients with Blau syndrome, compared with levels in the PBMCs of 5 controls, after cells were stimulated with muramyldipeptide, Pam_3Cys (a Toll-like receptor-2 [TLR-2] agonist), lipopolysaccharide (LPS), or with combinations of muramyldipeptide and either Pam_3Cys or LPS. In addition, Martin and colleagues presented 2 case reports in which recombinant human IL-1 receptor antagonist (anakinra) was not effective in treating Blau syndrome. Finally, the authors stated that Blau syndrome is not mediated by excess IL-1 activity.

We would like to present evidence that is consistent with the findings of Martin et al and to offer our own hypotheses. We also have data on IL-1β secretion levels in the PBMCs of 2 patients with Blau syndrome with an arginine-to-tryptophan mutation at position 334 of NOD-2 (R334W) (Figure 1A). These patients (whose cases have been reported previously [2]) had both been receiving prednisolone (15 mg/day [0.3 mg/kg]). The methods of isolation of PBMCs and the analysis of cytokine concentrations in culture supernatants were described by us in a previous report (3), and the analysis of patient materials was approved by the Human Research Ethical Committee of Shinshu University. We evaluated secretion levels of IL-1β, tumor necrosis factor α (TNFα), IL-6, and IL-8 in the culture supernatants of PBMCs that were left untreated for 8 hours or incubated with muramyldipeptide (10 ng/ml or 1 μg/ml) (a NOD-2 stimulatory ligand), LPS (0.1 ng/ml or 10 ng/ml) (a TLR-4 stimulatory ligand), or muramyldipeptide (10 ng/ml or 1 μg/ml) combined with a low amount of LPS (0.1 ng/ml). The data showed that IL-1β secretion from PBMCs isolated from patients with Blau syndrome remained

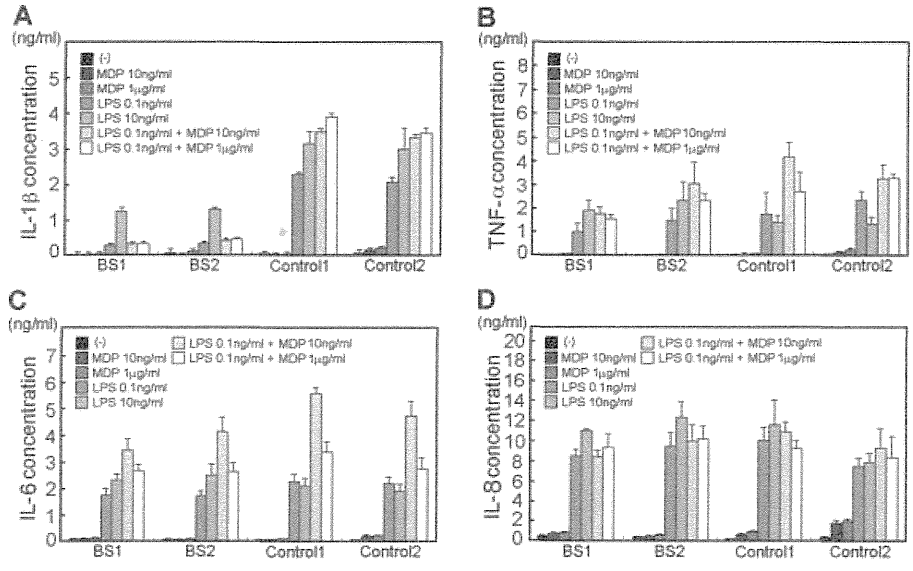

Figure 1. Secretion levels of interleukin-1β (IL-1β) (**A**), tumor necrosis factor α (TNFα) (**B**), IL-6 (**C**), and IL-8 (**D**) in peripheral blood mononuclear cells (PBMCs) isolated from the 2 patients with Blau syndrome (BS1 and BS2) and from 2 healthy controls. PBMCs were incubated with muramyldipeptide (MDP), lipopolysaccharide (LPS), or MDP combined with LPS, or were left untreated (−) for 8 hours. Secretion levels in the supernatants were measured by enzyme-linked immunosorbent assay. Values are the mean and SD from triplicate cultures.

undetectable without stimulation and was low after treatment with muramyldipeptide alone. These findings were the same as in healthy controls. PBMCs isolated from patients exhibited a lower response to LPS stimulation than cells from healthy controls. Notably, the synergistic stimulatory effect of the combination of muramyldipeptide and LPS on IL-1β secretion, which was observed in healthy controls, was not observed in patients with Blau syndrome, while the secretion levels of TNFα, IL-6, and IL-8 in the PBMCs of patients exhibited normal responses compared with healthy volunteers (Figures 1B–D). These observations are consistent with those reported by Martin et al (1).

IL-1β synthesis is known to be regulated by a 2-step process: transcriptional and translational regulation, and post-translational regulation. In the first step, activation of the transcription factor NF-κB leads to transcription of the proIL-1β gene, which can be translated to proIL-1β. The next step is maturation of proIL-1β by inflammasome, which is known to be an IL-1β–processing platform composed of Nod-like receptors, ASC, and caspase 1 (4). The secretion of IL-1β in PBMCs is known to be synergistically induced by muramyldipeptide and LPS. It has also been reported that this synergistic effect of NOD-2 and TLR on IL-1β maturation is caspase 1 dependent and that the activation of caspase 1 and the release of mature IL-1β by muramyldipeptide is NOD-2 dependent (5).

Mutated *NOD2* in patients with Blau syndrome is thought to be a constitutive active form of NOD-2, which has been found to lead to constitutive NF-κB activation in studies performed in vitro (6,7). The results of those studies do not contradict the data presented by Martin et al (1) or our own data (Figure 1), because the in vitro observation in HEK 293T cells transfected with the mutated form of *NOD2* (R334W) reflects primary initiated high-level NF-κB activation. Activation of NF-κB by constitutive activated mutated NOD-2 occurs via induction of a signaling complex, including RICK/RIP2 and IKK complex. Constitutive NF-κB activation then induces a negative feedback regulator, such as A20, a downstream regulator of RICK/RIP2 (8); therefore, we hypothesize that such a negative feedback regulator may affect inflammasome for IL-1β secretion either directly or indirectly. IL-1β secretion due to a synergistic effect of muramyldipeptide and LPS was not observed in PBMCs isolated from patients with Blau syndrome. Therefore, it is possible that the pathogenesis of Blau syndrome may be related to suppression of IL-1β synthesis.

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Using "real clinic" definitions to predict the course of juvenile dermatomyositis: comment on the article by Stringer et al

To the Editor:

We read with interest the recent article by Stringer et al, in which the authors analyze a cohort of patients from their center in order to determine whether the course of juvenile dermatomyositis (DM) can be predicted (Stringer E, Singh-Grewal D, Feldman BM. Predicting the course of juvenile dermatomyositis. Arthritis Rheum 2008;58:3585–92).

At present, there are no validated criteria for clinical remission and inactive disease in juvenile DM. In the study by Stringer et al, disease remission was defined as a clinical state in which rash is absent, there is no evidence of active myositis or arthritis, and the patient has not received immunosuppressive medications for a minimum of 6 months, and remission of skin disease was defined as the absence of heliotrope rash, Gottron's papules, and skin ulcers for at least 3 successive visits. We believe that using these definitions results in a significant number of patients who are classified as having "active" disease, when the standard clinical impression would be that the disease is in fact "inactive." In particular, classifying patients in whom there is clinical disease remission (no evidence of skin, muscle, or joint inflammation), but whose medications continue to be tapered slowly, as having active disease is problematic. The clinical treatment protocol used at the authors' center would require a minimum of 30 months of treatment, with methotrexate tapered over time. When taken together, the remission definition and the methotrexate tapering protocol exaggerated the median time to remission and caused the majority of patients in the study to be classified as having a chronic disease course.

Clinical and Genetic Features of Familial Mediterranean Fever in Japan

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ABSTRACT. ***Objective.*** Familial Mediterranean fever (FMF) is thought to be a rare disorder in Japan, and the clinical features of Japanese patients with FMF remain unclear. Our aim was to elucidate the clinical characteristics of FMF in Japanese patients.

Methods. We analyzed clinical and genetic data of 80 patients based on the results of a nationwide questionnaire survey and review of the literature.

Results. From clinical findings of 80 Japanese patients, high-grade fever was observed in 98.8%, chest attacks (pleuritis symptoms) in 61.2%, abdominal attacks (peritonitis symptoms) in 55.0%, and arthritis in 27.5%. Twenty-four percent of patients experienced their first attacks before 10 years of age, 40% in their teens, and 36% after age 20 years. Colchicine was effective in many patients at a relatively low dose (< 1.0 mg/day). AA amyloidosis was seen in only 1 patient. Common *MEFV* mutation patterns were E148Q/M694I (25.0%), M694I alone (17.5%), and L110P/E148Q/M694I (17.5%), and no patient carried the M694V mutation, the most common mutation in Mediterranean patients with FMF.

Conclusion. A larger than expected number of patients with FMF exist in Japan, and the clinical presentation of Japanese FMF patients seems to be relatively milder than those of Mediterranean FMF patients. AA amyloidosis rarely occurs in Japanese patients, probably due to difference in patterns of the *MEFV* genotype between Japanese and Mediterranean patients. (First Release June 15 2009; J Rheumatol 2009;36:1671–6; doi:10.3899/jrheum.081278)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER — *MEFV* GENE — JAPANESE PATIENTS
NATIONWIDE QUESTIONNAIRE — AA AMYLOIDOSIS

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrence of fever, polyserositis, and erysipelas-like skin lesions[1]. This disorder is the most common form of hereditary periodic fevers and there are over 100,000 patients around the world[2], but it predominately affects populations from the Mediterranean basin including non-Ashkenazi Jews, Arabs, Armenians, and Turks[1,3]. FMF is caused by mutations in the Mediterranean fever gene (*MEFV*) on chromosome 16p13.3, encoding a 781-amino acid protein denoted pyrin/marenostrin[4,5]. Over 170 sequence variants have been recorded in the dedicated database of the Registry of Familial Mediterranean Fever and Hereditary Auto-inflammatory Disorders Mutations, infevers (http://fmf.igh.cnrs.fr/ISSAID/infevers/). The variants V726A, M694V, M694I, M680I, and E148Q are the most frequent, accounting for 74% of all sequence variants[6]. Development of reactive AA amyloidosis is the most devastating complication of the disease[1,7]. The mainstay of therapy is daily colchicine, which prevents the attacks and the development of reactive AA amyloidosis[7].

In Japan, several patients with recurrent fever were clinically diagnosed as having FMF after 1976[8]. In 2002, the *MEFV* gene mutation was confirmed in a few Japanese patients with periodic fever[9,10], and since then a number of FMF patients diagnosed by DNA analysis have also been described. However, FMF is still recognized as quite rare in Japan, and it remains unclear whether the clinical features of Japanese patients are the same as those of Mediterranean patients or not. To elucidate the clinical features of Japanese patients with FMF, we studied clinical findings from 80 patients.

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MATERIALS AND METHODS

Patients. Clinical records of 80 Japanese FMF patients with *MEFV* gene mutations were studied. Clinical diagnosis of FMF was performed according to the Tel-Hashomer criteria[11]. Thirty-nine patients were diagnosed at Shinshu University Hospital between 2002 and 2007, including some previously reported[9,12-15]. Clinical data of the remaining 41 patients were obtained from a nationwide questionnaire survey (described below) and/or by review of the literature.

Nationwide questionnaire. To determine clinical features of patients, we carried out a nationwide questionnaire survey on FMF in 2006. The questionnaire was mailed to 1850 departments of internal medicine and pediatrics in Japan, asking about the number of FMF patients clinically diagnosed on the basis of the Tel-Hashomer criteria and/or the number of patients confirmed genetically, and the number of FMF patients with reactive systemic AA amyloidosis, between 1996 and 2006. Departments that answered that they had patients with FMF were sent another questionnaire asking for more detailed clinical information including the type of *MEFV* gene mutations. The protocol of these surveys was approved by the ethical committee of Shinshu University.

DNA testing of MEFV gene. DNA analysis of the *MEFV* gene was performed in patients with suspected FMF. Exon 2 and exon 10 with their flanking intronic sequences of the *MEFV* gene were amplified by polymerase chain reaction (PCR) using primers shown in Table 1. Exon 2 was amplified in 2 overlapping PCR fragments, exon 2a and exon 2b. Amplified PCR products were analyzed by direct sequencing (DNA Analyzer 3730xl; Applied Biosystems, Foster City, CA, USA). In patients without mutations in either exon 2 or 10 of the *MEFV* gene, other exons were also analyzed by direct sequencing after amplification of each exon[16]. An L110P mutation in exon 2 was analyzed by restriction fragment-length polymorphism (RFLP) analysis with *Sma* I restriction enzyme in addition to the DNA sequence analysis. An E148Q in exon 2 was also detected by RFLP with *BstN* I restriction enzyme after amplification using Exon2E148QF and Exon2E148QR as primers (Table 1).

Allele frequency analysis. Allele frequencies of L110P, E148Q, and M694I were analyzed in 51 healthy individuals and were compared to those in 39 patients with genetically diagnosed FMF at our institution. L110P and E148Q were analyzed by RFLP and M694I by the amplification refractory mutation system[17]. Differences in allele frequencies between the 51 healthy controls and the 39 FMF patients were compared statistically by the chi-square test.

Prior to the study, detailed informed consent was obtained from all patients following a clear explanation of the purpose of the study. Our genetic study protocol was approved by the local ethics committee.

RESULTS

The results of the questionnaire survey are shown in Table 2. Total response rate was 37.9%. The total number of patients who met the diagnostic criteria[11] was 131. Of the 131, 86 patients carried *MEFV* gene mutations (Table 2). Among these, detailed clinical data including the type of *MEFV* mutation were obtained from 58 patients (Figure 1); 39 of these patients were diagnosed at Shinshu University. The clinical data of the remaining 19 patients were obtained by the second survey; 13 of these patients had also been reported previously[10,18-22]. Unfortunately, further information such as the genotype in the other 28 of the 86 patients could not be obtained in the second survey.

In the nationwide survey, reactive AA amyloidosis associated with FMF was noted in 5 patients (3.8%; Table 2). One of them had already been described[10], but detailed clinical information on the other 4 patients could not be obtained from the second survey.

Clinical data. The results for the 58 patients whose clinical data were obtained by the nationwide survey (Table 2) and also those of 22 patients who had been described elsewhere[12,22-27] were studied (total 80 patients; Figure 1), as summarized in Table 3. Forty-nine patients (61.3%) did not have a family history suggestive of FMF (data not shown in the table). The male to female ratio was 33:47. The mean age at onset was 17.3 ± 10.7 years (data not shown); 19 patients (23.8%) experienced their first attacks before 10 years of age, 32 patients (40.0%) in their teens, 20 patients (25.0%) in their twenties, and 9 patients (11.3%) after age 30 years. Surprisingly, the age of onset was 53 years in one patient[26]. The mean age at diagnosis was 29.5 ± 13.7 years and the mean period from disease onset to diagnosis was 13.2 ± 11 years (data not shown).

High-grade fever (febrile attack) was the symptom seen most frequently (98.8%). Chest attack (pleuritis symptoms) was observed in 61.2% of patients and abdominal attack (peritonitis symptoms) in 55.0%. The frequency of arthritis was 27.5% and erysipelas-like erythema was seen in 10% of patients.

Colchicine was orally administered to 47 patients, and a favorable therapeutic effect was seen in at least 40 (85.1%). Information on efficacy was not obtained in the questionnaire survey in 5 patients. The daily dose of colchicine in 28 patients is shown Table 4, and 26 of these were treated with a relatively low dose (< 1.0 mg/day), among whom were 3 patients under 15 years of age. No patient required over 2.0

Table 1. Primers and polymerase chain reaction conditions.

	Primer	Annealing Temperature, °C
Exon2aF	5'-GCA TCT GGT TGT CCT TCC AGA ATA TTC C-3'	62
Exon2aR	5'-CTT TCC CGA GGG CAG GTA CA-3'	
Exon2bF	5'-CAG GCC GAG GTC CGG CTG CG-3'	62
Exon2bR	5'-CTT TCT CTG CAG CCG ATA TAA AGT AGG-3'	
Exon10F	5'-CCG CAA AGA TTT GAC AGC TG-3'	60
Exon10R	5'-TGT TGG GCA TTC AGT CAG GC-3'	
Exon2E148QF	5'-GCC TGA AGA CTC CAG ACC ACC CCG-3'	55
Exon2E148QR	5'-AGG CCC TCC GAG GCC TTC TCT CTG-3'	

Table 2. Results of the nationwide questionnaire survey.

Feature	Internal Medicine	Pediatrics	Total
Departments surveyed	1338	512	1850
Response rate (%)	437 (32.7)	264 (51.6)	701 (37.9)
Total no. of FMF patients	86	45	131
No. of FMF patients determined by gene analysis	49	37	86*
FMF patients with AA amyloidosis	4	1	5

* Clinical data of 58 out of 86 patients were available in this study.

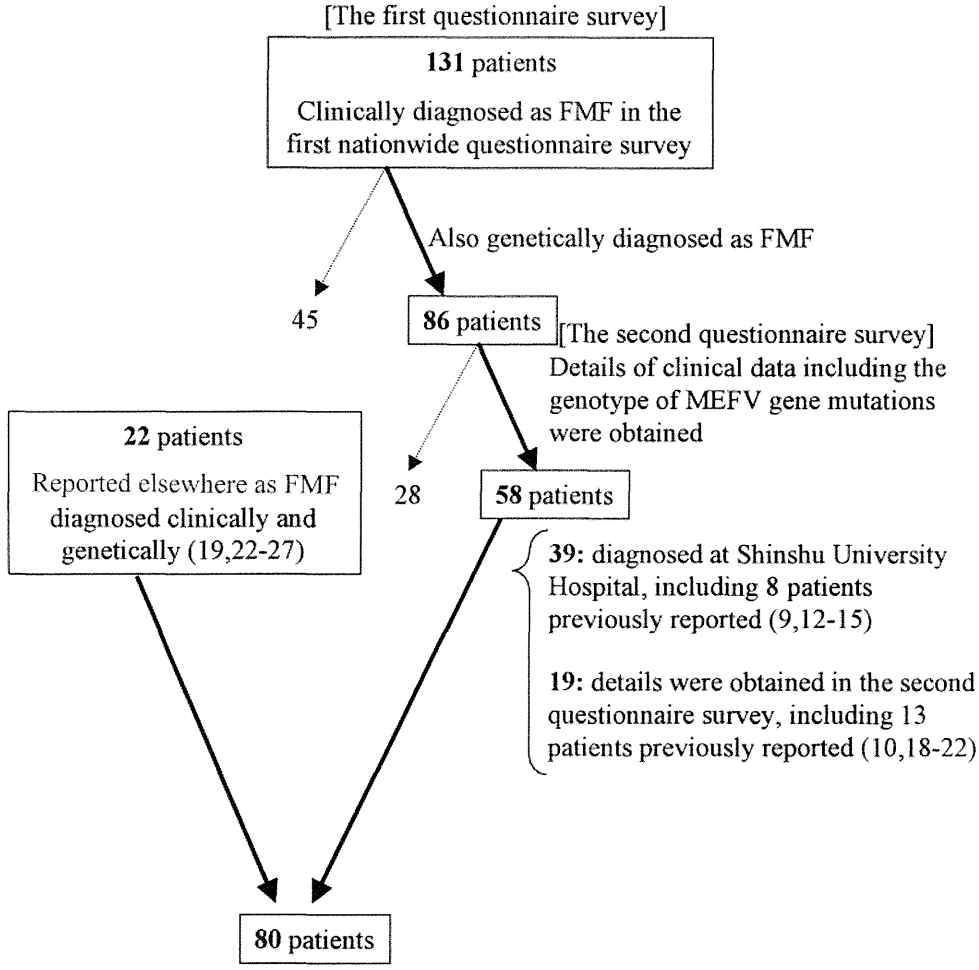

Figure 1. The process of patient selection in this study.

mg/day colchicine to prevent attacks. No effect was observed in 2 patients receiving 1.0 mg/day colchicine (Table 4), but the daily dose could not be increased due to severe diarrhea and bone marrow suppression[10,12,13]. At least 21 patients had not been treated with colchicine. As alternative treatments to colchicine, azelastine was used in one patient, with mild effectiveness, and a combined therapy with infliximab and low-dose methotrexate was effective in one patient[12,13]. In one patient interferon-α was also effective[25], and the herbal medicine "Sho-Saiko-To (TJ-9)" (Tsumura, Tokyo, Japan) was reported to be effective in another patient[20].

Five patients (6.3%) had also been diagnosed as having Behçet's disease (data not shown) before the *MEFV* mutation was identified. Of the 80 patients, only one (1.3%), who was homozygous for the M694I mutation, had reactive systemic AA amyloidosis[10].

MEFV gene mutations. The genotypes of the *MEFV* gene in the 80 patients are shown in Table 5. Common *MEFV* mutation patterns were E148Q/M694I (20 patients, 25.0%),