Familial Mediterranean Fever
A bird's eye view of the recent literature

edited by Eldad Ben-Chetrit

Diagnosis

Authors: Ozçakar ZB, Yalçınkaya F, Cakar N, Acar B, Bilgiç AE, Uncu N, Kara N, Ekim M, Kasapçopur O.
Title: Application of the new pediatric criteria and Tel Hashomer criteria in heterozygous patients with clinical features of FMF.
Eur J Pediatr 2011; 170: 1055-7. Epub 2011 Feb 2
Summary: Recently, a new set of criteria was established for the diagnosis of familial Mediterranean fever (FMF) in childhood. The aim of this study was to validate the new criteria set among heterozygous patients with clinical features of FMF. The study group consisted of 110 FMF patients, who had a mutation at a single allele. Patients were evaluated by the new criteria set and also by the Tel Hashomer criteria. According to the new criteria, the diagnosis of FMF was established by the presence of two or more of five criteria (fever, abdominal pain, chest pain, arthritis, family history of FMF). The sensitivity of the new criteria set and that of the Tel Hashomer criteria in this study group were found to be 93% and 100%, respectively.

Pathophysiology

Authors: Mitroulis I, Kourtzelis I, Kambas K, Chrysanthopoulou A, Ritis K.
Title: Evidence for the involvement of mTOR inhibition and basal autophagy in familial Mediterranean fever phenotype.
Hum Immunol 2011; 72: 135-8. Epub 2010 Dec 7.
Summary: mTOR signalling and autophagy modulate cellular responses to metabolic danger signals. This study, investigated the implication of mTOR inhibition and autophagy in FMF pathophysiology. mTOR inhibition induced *MEFV* gene expression in polymorphonuclear cells (PMNs) from healthy individuals, whereas it had no effect on PMNs from attack-free FMF patients. A significant reduction in pyrin levels in PMNs from FMF patients after mTOR inhibition was also observed. Pyrin levels in control PMNs remained unaffected. Moreover, the basal autophagic status in PMNs from FMF patients was reduced, as indicated by the lower LC3B-II/I ratio and ATG mRNA expression levels. The differential pyrin expression after metabolic stress induction and the impaired basal autophagy suggest a potential role in the triggering of FMF attacks.

Authors: Chae JJ, Cho YH, Lee GS, Cheng J, Liu PP, Feigenbaum L, Katz SI, Kastner DL.
Title: Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1β activation and severe autoinflammation in mice.
Immunity 2011; 34: 755-68. Epub 2011 May 19.
Summary: Whether FMF is due to the loss of an inhibitor of inflammation or to the activity of a proinflammatory molecule remained controversial. In this study the authors generated both pyrin-deficient mice and "knockin" mice harbouring mutant human B30.2 domains. Homozygous knockin, but not pyrin-deficient, mice exhibited spontaneous bone marrow-dependent inflammation similar to but more severe than human FMF. Caspase-1 was constitutively activated in knockin macrophages and active IL-1β was secreted when stimulated with lipopolysaccharide alone, which is also observed in FMF patients. It seem that gain-of-function pyrin mutations cause autoinflammatory disease and that the inflammasome is ASC-dependent and NLRP3-independent.

Authors: Tayer-Shifman OE, Ben-Chetrit E.
Title: Familial Mediterranean Fever and hypercoagulability.
Mediterr J Hematol Infect Dis 2011; c3(1): e2011017. Epub 2011 May 16.
Summary: Systemic inflammation, in general, may increase procoagulant factors, and decrease natural anticoagulants and fibrinolytic activity. Since FMF is a prototype autoinflammatory diseases it is anticipated to see more thrombotic events among FMF patients compared with healthy subjects. However, reviewing the current available literature and based upon the authors' experience, thrombotic events related purely to FMF are very rare. Possible explanation for this discrepancy is that along with the procoagulant activity during FMF acute attacks, anticoagulant and fibrinolytic changes are also taking place. Colchicine which is the treatment of choice in FMF may also play a role in reducing inflammation thereby decreasing hypercoagulability.

Clinical features

Authors: Padeh S, Livneh A, Pras E, Shinar Y, Lidar M, Feld O, Berkun Y.
Title: Familial Mediterranean fever in children presenting with attacks of fever alone.
J Rheumatol. 2010; 37: 865-9. Epub 2010 Mar 1.
Summary: In children, attacks of fever alone, or with headache and malaise, may precede other forms of attacks. The objective of the study was clinical and genetic characterisation of FMF and its development in paediatric patients who first presented with attacks of fever alone. Of 814 registered FMF children, fifty patients formed the study group and 234

patients the control group. In the study group, the first (febrile) attacks appeared at a younger age than in the control group and the diagnosis was made earlier. In the study group, attacks were shorter and homozygosity to the M694V mutation was more prevalent. Attack rate, colchicine dose, and the *MEFV* mutation carrier rates were comparable between the groups. In 40/50 (80%) of the patients with fever alone, serositis had developed over a course of 2.9 ± 2.2 years after disease onset. The study demonstrates that clinical heterogeneity at presentation is more likely to indicate a feature of a disease in development, rather than to mark distinct phenotypes of FMF.

FMF and other diseases

Authors: Koca SS, Etem EO, Isik B, Yuce B, Ozgen M, Dag MS, Isik A.
Title: Prevalence and significance of *MEFV* gene mutations in a cohort of patients with rheumatoid arthritis.
Joint Bone Spine 2010; 77: 32-5. Epub 2009 Dec 23.
Summary: The aim of this study was to explore the frequency and clinical significance of *MEFV* gene mutations in a cohort of Turkish patients with rheumatoid arthritis (RA). The study included 103 patients with RA and 103 age-, sex- and origin-matched healthy controls (HC). In all participants, genomic DNA was isolated and genotyped for *MEFV* gene mutations. In the RA group, disease activity was determined using the disease activity score-28 (DAS-28), and radiological damage was evaluated by the modified Larsen scoring method. Carrier rates of *MEFV* gene mutations were 26/103 (25.2%) and 24/103 (23.3%) in the RA and HC groups, respectively . In the RA group, while deformed joint count was significantly higher in the mutation carrier group than those of the non-carrier group ($p<0.05$), the level of C-reactive protein, DAS-28 and modified-Larsen scores were slightly but not significantly higher in the carrier group. The results of this study suggest that *MEFV* gene mutations appear to be an aggravating factor for the severity of RA.

Authors: Uslu N, Yüce A, Demir H, Saltik-Temizel IN, Usta Y, Yilmaz E, Beşbaş N, Gürakan F, Ozen H, Ozen S.
Title: The association of inflammatory bowel disease and *Mediterranean fever* gene (*MEFV*) mutations in Turkish children.
Dig Dis Sci 2010; 55: 3488-94. Epub 2010 Mar 21.
Summary: The authors investigated *MEFV* mutations and prevalence of FMF disease in Turkish children with IBD and their relationship with the disease severity. Sixteen patients with ulcerative colitis (UC), 14 with Crohn's disease (CD) and three with indeterminate colitis (IC) were enrolled in the study (median age 13 years, range 0.6–16 years, n=19 boys). MEFV mutations were detected in 17 of 66 (25.7%) alleles. Seven patients (four patients with CD, two with IC, and one with UC) were also diagnosed as FMF. FMF disease was found in seven of all IBD patients (21.2%) and four of them had CD. M694V was the leading mutation, and as a disease-causing mutation, it was found to be significantly more frequent in CD patients than UC patients. Demographics, laboratory evaluations, growth parameters, extraintestinal manifestations, and treatment with immunosuppressive agents other than steroids were comparable between the patients with and without FMF in most aspects. It seems that disease-causing *MEFV* mutations and FMF disease rate were increased among patients with IBD. The increase was prominent among CD patients, and not in UC patients.

Authors: Baruch Y, Dagan E, Rosner I, Fiorilli M, Gershoni-Baruch R, Rozenbaum M.
Title: *MEFV*, *TNFRSF1A* and *CARD15* mutation analysis in Behçet's disease.
Clin Exp Rheumatol 2011 Feb 17. [Epub ahead of print]
Summary: The authors evaluated the frequency of mutations and polymorphisms in *MEFV*, *TNFRSF1A* and *CARD15* in Israeli BD patients of either Jewish or Arab descent. Fifty-four BD patients (11 Jews and 43 Arabs), evaluated with respect to the entire spectrum of BD disease manifestations. Twelve patients (20.7%) displayed a single *MEFV* mutation and four patients (7.4%) had two mutated FMF alleles. Two patients (3.8%) carried a CARD15 variation and none carried a TNFRSF1A polymorphism. The frequency and distribution of mutated alleles between patients and controls was comparable ($p=0.27$). No statistically significant differences between carriers and non-carriers with respect to disease manifestations and severity score were calculated. The overall MEFV high carrier frequency in our cohort of BD patients seems to be attributed to their Mediterranean extraction rather than related to BD.

Authors: Rimar D, Rosner I, Rozenbaum M, Zuckerman E.
Title: Familial Mediterranean fever: an association with non-alcoholic fatty liver disease.
Clin Rheumatol 2011; 30: 987-91. Epub 2011 Mar 2
Summary: Twenty-seven patients (mean age, 48±18 years; F/M, 16:11) with FMF who were referred for assessment of chronic liver disease (CLD) were studied. Liver biopsy was performed in 21 of them. Patients with FMF and non-alcoholic fatty liver disease (NAFLD) were compared to matched controls from a cohort of 150 patients with NAFLD per liver biopsy but without FMF. Seven of ten patients who underwent mutation analysis for FMF were homozygous for M694V. In 15 patients, there was evidence of NAFLD. An additional five patients had "cryptogenic" cirrhosis. Comparing FMF patients with NAFLD to matched controls with NAFLD did not reveal excess of metabolic syndrome in FMF patients. Thus, 74% of the FMF patients had evidence of NAFLD. This high proportion of NAFLD in the cohort of FMF patients without overt metabolic syndrome may indicate an unappreciated novel association between FMF and NAFLD.

Authors: Yahalom G, Kivity S, Lidar M, Vaknin-Dembinsky A, Karussis D, Flechter S, Ben-Chetrit E, Livneh A.
Title: Familial Mediterranean fever (FMF) and multiple sclerosis: an association study in one of the world's largest FMF cohorts.
Eur J Neurol 2011; 18: 1146-50. Epub 2011 Feb 8.
Summary: The aim of the study was to describe and characterise the association between familial Mediterranean fever (FMF) and multiple sclerosis (MS) in 9 patients having both diseases. The onset of the FMF averaged 15.6 (3-37) years. Most patients suffered from abdominal and joint attacks, and 50% of the patients sustained a moderate to severe FMF. The onset of the MS was at an average age of 31.6 (17–50) years. Neurologic manifestations varied individually, without a dominant deficit, and the course was in a relapsing-remitting pattern in most. The median expanded disability status scale (EDSS) was in general of low score (3.0), apart from the patients who were homozygous for the M694V mutation, in whom the MS was more severe. Based on the current case series, the frequency of MS in the FMF population was 0.075%, twice higher the expected rate in the general population. Homozygosity for the *M694V MEFV* mutation may aggravate the phenotype of MS.

FMF treatment and outcome

Authors: Sahin M, Uğuz AC, Demirkan H, Nazıroğlu M.
Title: Colchicine modulates oxidative stress in serum and leucocytes from remission patients with Family Mediterranean Fever through regulation of Ca^{2}+ release and the antioxidant system.
J Membr Biol 2011; 240: 55-62. Epub 2011 Jan 20.
Summary: The effects of colchicine on oxidative stress and Ca^{2}+ release in serum and polymorphonuclear leucocytes (PMNs) of familial Mediterranean fever (FMF) patients with attack and remission periods was studied. Eighteen FMF patients and six age-matched healthy subjects participated. Colchicine (1.5 mg/day) was given to the FMF patients for 1 month. PMN cells, serum lipid peroxidation and intracellular Ca^{2}+-release levels were higher in the patients compared with the controls. However, they were lower in the remission group than in the attack group. Serum vitamin E and β-carotene concentrations were higher in the remission group than in the control and attack groups. The authors claimed that colchicine induced protective effects on oxidative stress by modulating vitamin E, β-carotene and Ca^{2}+-release levels in FMF patients with a remission period.

Authors: Akse-Onal V, Sağ E, Ozen S, Bakkaloglu A, Cakar N, Besbas N, Gucer S.
Title: Decrease in the rate of secondary amyloidosis in Turkish children with FMF: are we doing better?
Eur J Pediatr 2010; 169: 971-4. Epub 2010 Feb 24.
Summary: The most serious complication of FMF is the development of secondary amyloidosis. Besides genetic factors, environment has been implicated in the development of this complication. The main objective of this study was to analyse whether there has been a substantial decrease of secondary amyloidosis in Turkey and possible effective factors. For this purpose, clinical features of the patients diagnosed with secondary amyloidosis between the years 1978 and 1990 were compared with those diagnosed between 2000 and 2009. Median ages of the group diagnosed between 1978 and 1990 (n=115; 12.1% among a total of 947 renal biopsies) and diagnosed after 2000 (n=19; 2% among a total of 974 renal biopsies) were 12 and 13 years, respectively. There were no significant differences between the two patient groups according to gender, age, age of onset, disease duration, and disease severity. There was, however, a clear decrease in the percentage of biopsies with secondary amyloidosis from 12.1% (1978-1990) to 2% (after 2000; $p<0.001$).

Authors: Ozçakar ZB, Kadioğlu G, Siklar Z, Kavaz A, Nur Aksanal F, Berberoğlu M, Ekim M, Ocal G, Yalçinkaya F.
Title: The effect of colchicine on physical growth in children with familial Mediterranean fever.
Eur J Pediatr 2010; 169: 825-8. Epub 2009 Dec 17.
Summary: The aim of this study was to determine whether there is significant improvement in growth parameters in FMF patients after colchicine treatment. Patient files were retrospectively evaluated and patients that used colchicine for more than 1 year were included in the study. Demographic features, clinical findings before and after colchicine therapy, duration and dosage of therapy, weight, height, parentally adjusted height, and body mass index before and after colchicine therapy were noted and transformed into standard deviation scores (SDS). The study group consisted of 50 FMF patients. Median age at the time of diagnosis was 6.5 years. Median follow-up period was 3.6 years. Mean height SDS and mean parentally adjusted height increased significantly. Mean body mass index SDS also increased but this improvement was statistically insignificant.

Authors: Ozen S, Bilginer Y, Aktay Ayaz N, Calguneri M.
Title: Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine.
J Rheumatol 2011; 38: 516-8. Epub 2010 Dec 15.
Summary: Although colchicine is the standard therapy for preventing attacks and suppressing inflammation, 5%-10% of compliant patients are colchicine-resistant. In this study the authors report the effect of anti-tumour necrosis factor therapy (etanercept) and anti-interleukin 1 (IL-1) treatment (anakinra) in 6 cases resistant to colchicine therapy. Although etanercept lowered the number of attacks they still recurred. All 4 patients were switched to anakinra. In 2 patients anakinra completely resolved clinical and laboratory findings. The 4 patients under etanercept have been switched to anakinra which has reduced the number of attacks (to <1 per month) and lowered the levels of acute-phase reactants. In this small series, anakinra was successful in suppressing inflammation and decreasing the number of attacks in FMF.

Authors: Vandecasteele SJ, De Paepe P, De Vriese AS.
Title: Successful treatment of renal AA amyloidosis in familial Mediterranean fever with pegylated alpha-2a interferon. *Clin Nephrol* 2011; 75 (Suppl. 1): 1-3.

Summary: This is the first case of colchicine-resistant FMF in which a durable disease remission and regression of renal amyloidosis was induced by chronic treatment with pegylated interferon-alpha.