

cantly better than what we had reported earlier. It is most likely that the improvement in the outcome was the result of earlier recognition and treatment of this complication.

Authors: Iscan ZH, Vural KM, Bayazit M.

Title: Compelling nature of arterial manifestations in Behçet disease.

J Vasc Surg 2005; 41: 53-8.

Summary: This paper, from a large vascular surgery center in Turkey, described its experience on surgical treatment for

arterial complications of BS. Between 1990 and 2003, 20 patients (17 being men) had 34 vascular operations. The most common type arterial manifestation was the abdominal aortic aneurysm. The authors used synthetic and avoided autologous venous grafts.

The 10 year mortality rate (including operative mortality) was 70% and the 10 year complication free survival rate was 13%. Unfortunately the article did not give information about the post-surgical immunosuppressive treatment during the follow-up.

Familial Mediterranean fever.

A bird's eye review of the recent literature

edited by E. Ben-Chetrit

Pathogenesis

Authors: Diaz A, Hu C, Kastner DL, Schaner P, Reginato AM, Richards N, Gumucio DL.

Title: Lipopolysaccharide-induced expression of multiple alternatively spliced MEFV transcripts in human synovial fibroblasts: a prominent splice isoform lacks the C-terminal domain that is highly mutated in familial Mediterranean fever.

Arthritis Rheum 2004; 50: 3679-89.

Summary: The objective of this study was to investigate expression of the familial Mediterranean fever (FMF) gene (MEFV) in human synovial fibroblasts, chondrocytes, and peripheral blood leukocytes (PBLs). The subcellular localization of pyrin, the MEFV product, was determined in transfected synovial fibroblasts and HeLa cells with plasmids encoding pyrin isoforms. MEFV was expressed in synovial fibroblasts, but not in chondrocytes. Consensus and alternatively spliced transcripts were induced by lipopolysaccharide in synovial fibroblasts and PBLs. In transfected cells, the proteins encoded by all highly expressed splice forms were cytoplasmic. In contrast, native pyrin was predominantly nuclear in synovial fibroblasts, neutrophils, and dendritic cells, but was cytoplasmic in monocytes. The authors conclude that several MEFV transcripts are expressed and inducible in synovial fibroblasts. While recombinant forms of all major pyrin isoforms are cytoplasmic, native pyrin is nuclear in several cell types. This study confirms previous findings of Matzner's group in Jerusalem regarding the expression of MEFV gene in fibroblasts.

Genetics and phenotype-genotype correlations

Authors: Aldea A, Calafell F, Arostegui JI, Lao O, Rius J, Plaza S, Maso M, Vives J, Buades J, Yague J.

Title: The West Side Story: MEFVhaplotype in Spanish

FMF patients and controls, and evidence of high LD and a recombination "hot-spot" at the MEFV locus.

Hum Mutat 2004; 23: 399.

Summary: In this paper the authors analyzed intragenic MEFVSNPs in Spanish and Chueta (descendants of converted Jews) FMF patients and controls. They showed that there is a strong linkage disequilibrium (LD) at the MEFV locus and an intragenic recombination hot spot. They also found that the MEFV mutation spectrum in Spain is quite diverse and similar to those of France and Italy. However, the Chueta spectrum was poorer and closer to that of North African Jews, suggesting a direct connection with the Jewish diaspora.

Authors: Topaloglu R, Ozaltin F, Yilmaz E, Ozen S, Balci B, Besbas N, Bakkaloglu A.

Title: E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever.

Ann Rheum Dis 2005; 64: 750-2. E-pub 2004 Sept. 30.

Summary: The objective of this study was to evaluate the phenotypic features of patients with the E148Q mutation. The subjects included 26 patients who were homozygous for E148Q, 10 who were compound heterozygous for E148Q, and 8 complex cases. The results showed that although 4 of the 26 patients with E148Q/E148Q were asymptomatic at the time of evaluation, abdominal pain was present in 77% of the patients, fever in 66%, arthralgia in 50%, arthritis in 15.4%, and vomiting in 23.8%. None of the patients had amyloidosis, but 2 with E148Q/E148Q had a family history of amyloidosis and one had rapidly progressive glomerulonephritis secondary to vasculitis, which progressed to chronic renal failure. The authors conclude that patients homozygous for E148Q have a heterogeneous clinical presentation. Most are symptomatic and colchicine treatment is required in these patients. Yet the authors do not explain why 4 out of 26 E148Q homozygotes were asymptomatic. This fact suggests that an additional factor is needed in order to express the disease.

Authors: Tchernitchko D, Legendre M, Cazeneuve C, Delahaye A, Niel F, Amselem S.

Title: The E148Q MEFV allele is not implicated in the development of familial Mediterranean fever.

Hum Mutat 2003; 22: 339-40.

Summary: The E148Q (c.442G>C) sequence variant, which is situated in exon 2, is common but its role in FMF is controversial. In order to assess the implication of the E148Q variation in FMF, the authors investigated 233 patients of Sephardic Jewish origin living in France and 213 disease-free relatives of these patients. The frequency of the E148Q allele was found to be similar in the two groups (3.62% and 3.75%, respectively, $p=0.93$). Most importantly, the frequency of the M694V/E148Q compound heterozygous genotype was comparable between the patient group (3.9%) and the healthy relatives group (4.2%, $p=0.85$). This population-based study therefore strongly supports the hypothesis that E148Q is merely a benign polymorphism and not a disease-causing mutation. Considering this variant as a mutation may lead to false positive diagnoses and to neglecting the likely existence of genetic heterogeneity in FMF.

Authors: Medlej-Hashim M, Delague V, Chouery E, Salem N, Rawashdeh M, Lefranc G, Loiselet J, Megarbane A.

Title: Amyloidosis in familial Mediterranean fever patients: correlation with MEFV genotype and SAA1 and MICA polymorphisms effects.

BMC Med Genet 2004; 5: 4.

Summary: In this paper the authors attempted to determine the correlation between the MEFV genotype and the occurrence of amyloidosis in FMF patients, in addition to studying the modifying effects of the SAA1 (type I serum amyloid A protein) and MICA (Major Histocompatibility Complex (MHC) class-I-chain-related gene A) genes on this severe complication. They found that the M694V and V726A allelic frequencies were significantly higher and lower, respectively, in the group with amyloidosis compared to the control FMF group. The beta and gamma SAA1 alleles were more frequently encountered in the group without amyloidosis, whereas the alpha allele was significantly more frequently observed in FMF patients with amyloidosis ($p < 0.025$). All MICA alleles were encountered in both patient groups, but none of them was significantly associated with amyloidosis. They conclude that the SAA1 beta and gamma alleles have a protective effect on the development of amyloidosis and that the MICA genes do not have a modifying effect on the development of amyloidosis.

Author: Majeed HA, El-Khateeb M, El-Shanti H, Abu Rabaiha Z, Tayeh M, Najib D.

Title: The spectrum of familial Mediterranean fever gene mutations in arabs: report of a large series. *Semin Arthritis Rheum* 2005; 34: 813-8.

Summary: The objectives were to identify the frequency and distribution of familial Mediterranean fever (FMF) gene

(MEFV) mutations in Arab patients. Screening for 5 mutations, namely M694V, V726A, M694I, M680I, and E148Q, was performed by the amplification refractory mutation system (ARMS) for the first 4 and by restriction endonuclease testing for E148Q. Analysis of 407 unrelated patients revealed that 239 (59%) had 1 or 2 mutations and 168 (41%) had none of the studied mutations. Of those with the mutations, 92 were homozygous, 53 were compound heterozygotes, 3 had complex alleles, and 91 patients had only 1 identifiable mutation. Of the mutations, M694V, V726A, M694I, M680I, and E148Q accounted for 38%, 26%, 14%, 10% and 13%, respectively. These data indicate that the 5 MEFV mutations are well distributed in Arabs. M694V is the most common mutation in Arab patients with FMF and seems to be associated with the development of amyloidosis. The surprising result here is the lack of mutations in more than 40% of the FMF patients investigated.

Treatment

Authors: Lidar M, Scherrmann JM, Shinar Y, Chetrit A, Niel E, Gershoni-Baruch R, Langevitz P, Livneh A.

Title: Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socio-economic characterization.

Semin Arthritis Rheum 2004; 33: 273-82.

Summary: In this study the authors sought to identify the ethnic, clinical, genetic, and pharmacokinetic correlates of colchicine treatment failure in patients with familial Mediterranean fever (FMF). They found that non-responders were usually from lower socioeconomic backgrounds, had less education, and suffered from a more severe form of the disease. A statistically significant 2-fold elevation in colchicine concentrations in the mononuclear cells (MNC) of responders was also found. They conclude that colchicine treatment failure in FMF is associated with inadequate colchicine MNC concentrations, probably resulting from a genetic defect unrelated to the underlying FMF. These results also suggest that the low levels of colchicine in MNC could reflect non-compliance due to the patients' low education, etc.

Authors: Ben-Chetrit E, Fischel R, Hinz B, Levy M.

Title: The effects of colchicine and hydroxychloroquine on the cyclo-oxygenases COX-1 and COX-2.

Rheumatol Int 2005; 25: 332-5. E-pub 2004 Feb. 13.

Summary: The aim of this study was to test whether colchicine and hydroxychloroquine have inhibitory effects on cyclo-oxygenases (COX). The results showed that colchicine did not have an inhibitory effect on COX. At relatively high concentrations hydroxychloroquine had a mild inhibitory effect. As expected celecoxib, etodolac, and nimesulide did have an inhibitory effect on the cyclo-oxygenases. The authors conclude that neither colchicine nor hydroxychloroquine exert their anti-inflammatory effect through the inhibition of cyclo-oxygenases.

End stage renal disease and transplantation

Authors: Altiparmak MR, Pamuk ON, Ataman R, Serdengecti K.

Title: Continuous ambulatory peritoneal dialysis in familial Mediterranean fever. *Nephron Clin Pract* 2004; 98: c119-23.

Summary: In this study the authors tried to evaluate the efficacy of continuous ambulatory peritoneal dialysis (CAPD) in FMF-amyloidosis patients with ESRD. Forty age- and sex-matched patients undergoing CAPD at their centre between 1996 and 2002 were included in the study. Of these, 10 had FMF-amyloidosis, 10 had diabetes mellitus (DM), 10 had chronic glomerulonephritis (CGN) and 10 had chronic interstitial nephritis (CIN). The efficiency of CAPD, the development of complications, the presence of other diseases and the survival rate were compared. The results showed that there was no significant difference between the FMF-amyloidosis group and other groups in terms of the efficiency of CAPD, peritoneal function, complications or survival. DM patients had a shorter survival period compared with CGN and CIN patients ($p < 0.05$), but there was no difference in survival between FMF-amyloidosis patients and the other groups ($p > 0.05$). These findings are of interest since it is known that peritoneal dialysis is a major cause of peritonitis and intestinal obstruction and in FMF one would theoretically expect more complications of this kind.

Authors: Keven K, Sengul S, Kutlay S, Ekmekci Y, Anadol E, Nergizoglu G, Ates K, Erturk S, Erbay B.

Title: Long-term outcome of renal transplantation in patients with familial Mediterranean fever amyloidosis: a single-center experience.

Transplant Proc 2004; 36: 2632-4.

Summary: The aim of this study was to determine the short- and long-term results of renal transplantation in patients with FMF amyloidosis. The authors compared the outcomes of 17 patients with FMF amyloidosis among 431 (3.9%) transplants with 209 control patients. They observed 93% and 94% graft and patient survivals at 1 year, and 89% and 90% at 5 years. Also, the mean serum creatinine levels at 1 and 5 years post-transplant were similar. Recurrence of amyloidosis was documented in two allograft recipients presenting with nephrotic range proteinuria (12%), one of whom lost the allograft due to recurrence. They conclude that the long-term outcomes of transplantation in patients with amyloidosis secondary to FMF is similar to that in the general transplant population and maintenance colchicine, even at low dose, appears to effectively prevent the recurrence of amyloidosis in the allograft.

Authors: Sherif AM, Refaie AF, Sheashaa HA, El-Tantawy AE, Sobh MA.

Title: Long-term evaluation of neuromyopathy in live donor FMF amyloidotic kidney transplant recipients.

Am J Nephrol 2004; 24: 582-6. E-pub 2004 Nov 19

Summary: Neuromyopathy has been reported to be a problem among live donor familial Mediterranean fever (FMF)

amyloid kidney transplant recipients. In this study the authors addressed this issue on a long-term basis. Fourteen FMF amyloid live donor kidney transplant recipients with a mean post-transplant follow-up period of 82.43 ± 50.1 months in comparison to a control group of 19 non-amyloid renal transplant patients were subjected to thorough neurological examination, and laboratory and electrophysiologic studies. Results showed that the two groups were comparable with regard to mean serum creatinine levels and serum creatine phosphokinase. Electrophysiologically demonstrated neuromyopathy was more liable to occur in long-term live donor FMF amyloidotic kidney transplant recipients than in the other non-amyloidotic kidney transplant recipients, even if they show no clinical manifestations nor raised creatine phosphokinase levels.

Reproductive system

Authors: Ben-Chetrit E, Berkun Y, Ben-Chetrit E, Ben-Chetrit A.

Title: The outcome of pregnancy in the wives of men with familial Mediterranean fever treated with colchicine.

Semin Arthritis Rheum 2004; 34: 549-52.

Summary: The objective of the study was to evaluate the outcome of pregnancies of normal women married to men with familial Mediterranean fever (FMF), some of whom were on colchicine therapy when their babies were conceived. The authors followed the outcome of pregnancies and deliveries of 60 wives of FMF patients; 53 of the husbands were taking colchicine during that time. As a control group they screened the outcome of pregnancy and delivery from 230 healthy women married to healthy men. The results showed that 60 FMF patients' wives had 222 pregnancies, of which 206 ended in term delivery with 209 live births. Sixteen pregnancies ended in spontaneous abortions (7%). Three of the infants in the study group were born with congenital malformations. In the control group of 788 pregnancies, 127 ended in abortions (16%). Six of these newborns were born with congenital malformations. The rate of late abortions (second trimester) in both groups was comparable. These results indicate that neither FMF nor colchicine increases the rate of abortions or congenital malformations.

Interaction with other inflammatory diseases

Authors: Fidler H, Chowers Y, Ackerman Z, Pollak RD, Crusius JB, Livneh A, Bar-Meir S, Avidan B, Shinhar Y.

Title: The familial Mediterranean fever (MEVF) gene as a modifier of Crohn's disease.

Am J Gastroenterol 2005; 100: 338-43.

Summary: The authors investigated the prevalence of MEFV mutations in Jewish non-Ashkenazi patients with Crohn's disease (CD) and their putative effect on CD presentation. A germline DNA of 105 Israeli CD patients of non-Ashkenazi and mixed Ashkenazi-non-Ashkenazi ethnic background was analyzed for the three most common MEFV mutations: M694V, V726A, and E148Q. Five patients (4.7%)

with a clinical diagnosis of FMF were included. Results showed that the overall prevalence of mutation carriers among non-FMF-CD patients was 13% (13/100). A stricturing disease pattern was observed in 56% (10/18) of all carriers, FMF-CD, and non-FMF-CD patients, and in 25% (22/87) of the non-carriers. The prevalence of fistulas was comparable in the two groups. Extra-intestinal manifestations were significantly more frequent among carriers than non-carriers (65% vs 32%). No differences were observed in the disease's location or severity. The authors conclude that MEFV mutations are not associated with CD susceptibility, although the presence of these mutations does appear to be associated with a stricturing disease pattern and extra-intestinal disease manifestations of CD.

Authors: Rabinovich E, Livneh A, Langevitz P, Brezniak N, Shinar E, Pras M, Shinar Y.

Title: Severe disease in patients with rheumatoid arthritis carrying a mutation in the Mediterranean fever gene.

Ann Rheum Dis 2005; 64: 1009-14.

Summary: The objective of this study was to determine if known mutations of MEFV are associated with rheumatoid arthritis (RA) morbidity or can modify RA severity. The frequency of the 3 most common MEFV mutations: M694V, V726A, and E148Q, was determined in 98 Israeli patients with RA (74 women, 24 men) and compared with the frequencies in 100 healthy subjects matched for origin. RA severity was determined using a new clinical score of 126 grades. 17/98 (17%) patients with RA (all women) were heterozygous for common MEFV mutations, predominantly E148Q (12 patients), and one patient was homozygous for the V726A mutation. The overall mutation rate was comparable between patients with RA and healthy subjects. Patients carrying a mutation had a higher median severity score than the non-carrier group (42 vs 29, $p=0.0005$). The authors conclude that the MEFV, and particularly the E148Q, mutation is an independent modifier of the clinical manifestations of RA.

Authors: Aganna E, Hawkins PN, Ozen S, Pettersson T, Bybee A, McKee SA, Lachmann HJ, Karenko L, Ranki A, Bakkaloglu A, Besbas N, Topaloglu R, Hoffman HM, Hitman GA, Woo P, McDermott MF.

Title: Allelic variants in genes associated with hereditary periodic fever syndromes as susceptibility factors for reactive systemic AA amyloidosis.

Genes Immun 2004; 5: 289-93.

Summary: The authors investigated the hypothesis that low-penetrance mutations in genes (TNFRSF1A, MEFV and NALP3/CIAS1) associated with hereditary periodic fever syndromes (HPFs) might be risk factors for AA amyloidosis among patients with chronic inflammatory disorders. They found that 4 of 67 patients with RA and amyloidosis had

MEFV variants compared with none of 34 RA patients without amyloid. The E148Q variant of MEFV was present in 2 of 3 patients with TNF receptor-associated periodic syndrome (TRAPS) complicated by amyloid in two separate multiplex TRAPS families with 5 and 16 affected members respectively, and the single patient with Muckle-Wells syndrome who had amyloidosis was homozygous for this variant. The R92Q variant of TNFRSF1A was present in 2 of 61 juvenile idiopathic arthritis (JIA) patients with amyloidosis, and in none of the 31 non-amyloidotic JIA patients. Although allelic variants in HPFs genes are not major susceptibility factors for AA amyloidosis, low-penetrance variants of MEFV and TNFRSF1A may have clinically significant proinflammatory effects.

Review

Authors: Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, Tutar E, Ozen S, Topaloglu R, Yilmaz E, Arici M, Bakkaloglu A, Besbas N, Akpolat T, Dinc A, Erken E; Turkish FMF Study Group.

Title: Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study.

Medicine (Baltimore) 2005; 84: 1-11

Summary: This is the largest series of patients with FMF ($n = 2,838$) reported from a single country. The features of the disease in the Turkish population are described and the authors show that amyloidosis is still a substantial problem.

Miscellaneous

Authors: Sayarlioglu M, Cefle A, Inanc M, Kamali S, Dalkilic E, Gul A, Ocal L, Aral O, Konice M.

Title: Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases.

Int J Clin Pract 2005; 59: 202-5.

Summary: Records of 401 patients (female/male: 204/197) who were followed-up between 1990 and 1999 were reviewed according to a pre-defined protocol. The demographic and clinical features of adult-onset FMF patients were compared to those of patients with a disease onset before 20 years of age. There were 57 patients (14%) who experienced symptoms of FMF at 20 years of age; 34 of them (8.5%) reported their first attack between the ages of 20 and 29 years; 18 (4.5%) between 30 and 39 years of age; and 5 patients (1.25%) had their first attack after 40 years of age. Arthritis and erysipelas-like erythema were significantly less frequent in patients with adult-onset FMF compared to patients with a disease onset before 20 years of age. Adult-onset FMF may be a form of disease with distinct clinical, demographic and molecular characteristics.