Clinical Review

Familial Mediterranean Fever

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ABSTRACT

Familial Mediterranean Fever is a genetic disorder frequently diagnosed among the Arabs. It is also prevalent among Jews, Armenians and Turks. The clinical picture consists of febrile and painful attacks that differ in quality across patients and even within the same patient. There may be accompanying joint pain, chest pain, skin manifestations and other findings, and amyloidosis may occur in some patients as a complication. The primary treatment is Colchicine, which decreases the frequency of the attacks and prevents the occurrence of amyloidosis. The gene responsible for Familial Mediterranean Fever, MEFV, has been mapped and cloned and mutations were identified within its coding sequence. It encodes a protein that is expected to be a down regulator of inflammation. The spectrum of mutations in the Arabic population is partially studied. There are still several issues to be solved before we fully understand the disorder, and to enable us to confront it and decrease the morbidity and mortality inflicted by it.

Keywords: Familial Mediterranean Fever, abdominal pain, colchicine.

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Familial Mediterranean Fever (FMF) was first described as a distinct disease entity, under the name of benign paroxysmal peritonitis in 1945.[1] Although early on, it had several names, in the early sixties, the international medical community adopted the name suggested by the team led by Heller,[2] which is, FMF. There are 3 classical aspects of the disorder that pertain to its name. First, Familial, as it is autosomal recessive,[3] however, about half of the patients do not report a family history of the disorder. Second, Mediterranean, as it is prevalent in Mediterranean populations, namely, Jews (mainly non-Ashkenazi), Armenians, Turks and Arabs.[4-13] Third, Fever, which is the most common component of the disorder.[3] However, some patients do not realize that they are febrile during the attacks.

The clinical picture. The clinical picture consists of febrile and painful attacks that are usually of acute onset, variable frequency, and without a noticeable triggering factor but often occurring with menstruation, emotional stress or strenuous physical activity. The pain is usually severe occurring in the abdomen, chest and joints due to inflammation of the peritoneum, pleura and synovial membrane. The attacks last from 12-72 hours and abort abruptly but the arthralgia, if present, may last longer. The attacks start, most commonly, during childhood or adolescence, with about 80% of patients presenting their symptoms before the age of 20 years and very few after the age of 40 years.[5,6,11-14] The clinical picture, intensity of symptoms and frequency varies from one attack to another and from one patient to another even within the same family.[3] All patients suffer from abdominal pain at one point, and it is reported in 50% of patients as the first symptom.[13] It can be diffuse or localized, ranging in intensity from mild bloating to real peritonitis with rigidity, tenderness and rebound tenderness.[3] There can be constipation and the history may include a laparotomy for appendectomy.[3] Chest pain is present in about 50% of attacks, usually in the form of unilateral pleurisy with diminished breath sounds, friction rub and may be effusion or collapse.[5,6,13,15] Joint pain is present in about 50-75% of attacks and

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it is in the form of arthritis or arthralgia.[5,12,15,16] The arthritis is usually monoarticular affecting the knee, hip or ankle joint.[5,12,15,16] Some patients develop protracted arthritis, synovitis, muscle atrophy, erosions and juxta-articular osteoporosis.[17-20] The most characteristic skin lesion is the erysipelas-like erythema, occurring in 3-45% of attacks.[21,22] It is a unilateral or bilateral, red, warm, swollen lesion about 10-15 cm in diameter, occurring below the knee or on the dorsum of the foot. The laboratory findings are non-specific and include leukocytosis with left shift, elevated erythrocyte sedimentation rate (ESR), high acute phase reactant titres like C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, C3 and C4. There maybe transient albuminuria and microscopic hematuria. In between attacks patients are free of symptoms. There may be slight discomfort, slight fever, splenomegaly, anemia, increased fibrinogen and increased immunoglobulins. Uncommon manifestations include acute scrotal inflammation;[23-26] myalgia that can be mild, diffuse and of a short duration or protracted;[27,28] headache, with meningeal irritation and increased cerebrospinal fluid (CSF) proteins and cells;[29-31] impaired female fertility;[32,33] pericarditis;[34,35] vasculitis,[10,13,22,36] purpuric lesions[22] and glomerulo-nephritis or nephropathy.[37-40] One of the significant impacts of the disorder on the affected individual is the occurrence of amyloidosis as a complication. It is due to the deposition of AA protein, which is a cleavage product of SAA by the liver (acute phase reactant). Chemically, it is the same type of reactive amyloidosis, which takes place with chronic infections such as tuberculosis, bronchiectasis and rheumatoid arthritis.[41] Amyloid A deposits in kidneys, adrenal glands, intestine, spleen, liver, lung, thyroid, heart, stomach and testes. Clinically, its deposition in the kidneys leads to persistent proteinuria, nephrotic syndrome and eventual renal failure.[13] Intestinal malabsorption and adrenal insufficiency became recognized after the establishment of chronic renal dialysis as a treatment for renal failure and thus the prolongation of the lives of those affected. Routine urinalysis looking for early albuminuria should be followed by renal biopsy, rectal biopsy, bone marrow biopsy, abdominal fat aspiration or gingival biopsy.[42-44] The biopsy should be stained with congo red and viewed under polarized light where AA gives an apple green colour. The treatment for amyloidosis is by hemodialysis and renal transplantation. Colchicine plays an important role in the prevention of amyloidosis and its reaccumulation in a grafted organ.[45]

Therapy. Two initial publications introduced Colchicine as the primary therapy to reduce the frequency of FMF attacks.[46,47] Its efficacy was established by few placebo-controlled trials.[48-50] A daily regimen of 1-2 mg of oral Colchicine, introduced gradually, remains the recommended treatment since its introduction.[51] It has been shown that this regimen is beneficial, also for the prevention of amyloidosis in all patients,[10,52] in those already exhibiting proteinuria,[53] and for the prevention of the reaccumulation of AA in a transplanted kidney.[45] While being a miracle therapeutic option for FMF, Colchicine is not without its side effects.[51] Many patients suffer from diarrhea and gastrointestinal upset but seem to tolerate it better when it is introduced gradually.[51] In addition, Colchicine has been shown to induce lactose intolerance in FMF patients, which can be remedied by a lactose free diet and antiflatulents.[54] Uncommon side effects include myopathy and peripheral neuropathy but mostly in older patients with impaired renal function.[55] Although, it was reported that there was no teratogenic risk in 231 pregnancies in FMF patients on Colchicine, the same group later reported that the incidence of trisomy 21 was twice the expected.[32] It is generally recommended to decrease the Colchicine dose during pregnancy, if possible, and to perform amniocentesis early in the 2nd trimester. The concentration of Colchicine in breast milk is very low, thus it seems safe for the child during lactation. While oral Colchicine has few risks, the intravenous administration of the drug carries major hazards and can lead to multiple organ failure and even death.[56-59] Interferon α is now considered as an adjuvant therapy for acute attacks in FMF patients who still suffer attacks while on Colchicine, or are resistant to the drug.[60] Placebo controlled trials are still needed to evaluate its real value in the management of FMF attacks.

The gene. The successful mapping of the FMF gene was preceded by exclusion, using linkage analysis, of the AA gene, as well as, several other candidate genes that play a role in the inflammatory response.[61-63] Linkage was tentatively suggested between the FMF gene and deoxyribonucleic acid (DNA) markers on chromosome 17, which proved to be a type 1 (α) error.[64] The gene, then named MEF, was finally mapped to the short arm of chromosome 16, with clear evidence for genetic homogeneity of the disorder.[65-67] The genetic distance was determined at about 9 cM.[68] The region containing the gene was then reduced to one million base pairs by linkage analysis, homozygosity studies and linkage disequilibrium.[68-71] Polymorphic markers pulled out from a highly redundant contig spanning the one million base pairs further reduced the region to a 285 Kb fragment,[72] while the other group managed to reduce the region to 250 Kb.[73] Analysis of historical recombinant haplotypes further narrowed the candidate interval to a 200 Kb region.[72,73] Utilizing different sophisticated molecular biology methodologies the region containing the gene was narrowed down to a 60-115 Kb.[74,75] This lead to the final cloning of the gene for FMF, now called

MEFV, by the 2 consortia independently and simultaneously.[74,75] The gene is made of 10 exons, the complementary DNA (cDNA) is 3505 nucleotides long and it encodes for a 781 amino-acid long protein.[74,75] With the cloning of the gene, 4 missense mutations, clustered in the 10th exon were identified, each of which is associated with a distinct haplotype.[74,75] The identification of other mutations in the gene further established MEFV as the gene responsible for FMF.[76,77]

The spectrum of mutations. Up until now, about 25 different mutations and polymorphisms are identified, most of them clustered in the 10th exon of MEFV.[74-79] Due to the high prevalence of the disorder in the populations under study, it is sometimes difficult to distinguish a polymorphism from a disease causing mutation.[80] Table 1 shows the 17 different mutations identified up to the end of the year 1999. The spectrum of mutations amongst the Arabs has not been adequately studied. The French consortium identified the M694I as a mutation corresponding to the ARA2 haplotype.[74] Bernot et al identified several mutations in Arabs, A744S was present in one patient, E148Q was found on the same chromosome with another mutation, E148Q was homozygous in one patient and the E148Q and the V726A were present on the same chromosome in Druze patients.[76] Booth et al, identified 3 mutations in 2 Iraqi patients and one mutation in a Jordanian patient.[77] In one study that included 25 Arabs, mutations were found in 78% of chromosomes.[81] On the expansion of the same group of Arabic patients (60 patients), mutations were only found in 60% of chromosomes.[82]

Table 1 - Common mutations identified in the MEFV gene.

	Mutation	DNA site	Test
1	E148Q	442 G-C	RE
2	E167D	501 G-C	ARMS
3	T267I	800 G-A	
4	P369S	1105 C-T	RE
5	R408Q	1223 G-A	
6	F479L	1437 C-G	
7a	M680I	2040 G-C	ARMS
7b		2040 G-A	RE
8	T681I	2042 C-T	
9	I692de1	2076-2078	
10	M694de1	2078-2080	
11	M694V	2080 A-G	ARMS
12	M694I	2082 G-A	RE
13	K695R	2084 A-G	ARMS
14	V726A	2177 T-C	ARMS
15	A744S	2230 G-T	ARMS
16	R761H	2282 G-A	ARMS

DNA - Deoxyribonucleic acid;
G - Guanine; C - Cytosine; A - Adenine; T - Thymine
RE - Restriction Endonuclease Analysis
ARMS - Amplification Refractory Mutation System

A somewhat detailed study from Jordan found mutations in about 50% of the chromosomes.[83] Two studies from Jordan reported mutations in only 45% of chromosomes but provided preliminary data on phenotype - genotype correlations.[84,85]

Phenotype/genotype correlations. One of the aims of understanding FMF pathogenesis is to examine if a specific mutations is associated with a specific disease phenotype. One study correlated homozygosity for M694V with a more severe disorder in a non-Ashkenazi Jewish population.[86] Another study carried out on a wider spectrum of populations failed to show any correlation between a specific mutation and the severity of the symptoms but showed a correlation between homozygosity for M694V and the incidence of amyloidosis.[87] One study showed a tendency for higher prevalence of amyloidosis and arthritis amongst Armenian patients homozygous for the M694V mutation.[79] It can now be deduced that phenotype - genotype correlations are not consistent across the different populations in whom the disease occurs with considerable frequency.

The protein. The protein has been named pyrin by the International consortium and marenostrin by the French consortium (after the Latin name for the Mediterranean sea; Mare Nostrum).[74,75] The protein has domains with some homology to already existing human and other organism proteins.[74,75] Based on the structure of the gene, the structure of the protein and its homology to other proteins, it is suggested that pyrin/marenostrin acts in the nucleus as a transcription factor and is probably a direct or indirect down regulator of inflammation.[3,74,75]

In conclusion, the identification of the MEFV gene has shed some light on the molecular basis of inflammation. However, this giant step has just made it clear that there is still a lot to accomplish in the understanding of FMF before we can conquer the disease. A more comprehensive mutational inventory will contribute, not only to the clinical diagnosis, but may direct the studies towards the understanding of the function of the protein, pyrin/marenostrin, and the role it plays in the control of inflammation. Animal models, whether naturally occurring or produced transgenically, may be another route towards the delineation of the protein function and its interactions with other proteins. In fact, the final goal would be to outline an inflammatory pathway in which the pyrin/marenostrin plays a role, and devise methods to counteract defaults in this pathway. This final goal can only be achieved by putting all the pieces of the puzzle together armed with clinical, molecular and epidemiologic tools for the dissection of this complex disorder.

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