Prevalence of Ischemic Heart Disease in Patients with Familial Mediterranean Fever

Pnina Langevitz MD[1], Avi Livneh MD[1], Lily Neumann PhD[2], Dan Buskila MD[3], Joshua Shemer MD[1], David Amolsky MD[1] and Mordechai Pras MD[1]

[1]Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer and Sackler Faculty of Medicine, Tel Aviv University, and [2]Department of Epidemiology and [3]Rheumatic Disease Unit, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

Abstract

Background: Familial Mediterranean fever is a genetic disorder manifested by recurrent attacks of peritonitis, pleuritis and arthritis, and characterized by clinical, histological and laboratory evidence for localized and systemic inflammation. Colchicine treatment usually prevents the attacks and the associated inflammation. Inflammation may play an important role in the initiation and progression of atherosclerosis and ischemic heart disease.

Objective: To study the effect of inflammation and its prevention on the occurrence of IHD, using FMF as a model.

Methods and Patients: We studied the presence of IHD and its risk factors in 290 FMF patients aged 40 years or more, and in two control groups – 233 spouses of the FMF patients, and 126 patients with inflammatory diseases obtained from other outpatient clinics. FMF patients were also compared with age and gender-matched individuals from the population reference data of the Israel Ministry of Health.

Results: The prevalence of IHD in FMF patients was significantly lower than in the group of controls from other outpatient clinics (15.5% vs. 30.2%, $P < 0.05$) and comparable with their spouses (11.2%) and with the matched general population in Israel (16%).

Conclusions: These findings suggest that despite the evidence of recurrent inflammation, colchicine-treated FMF patients are not more predisposed to IHD than the normal population.

IMAJ 2000;2:9-12

Familial Mediterranean fever is an autosomal recessive disease found more commonly among Sephardic and North African Jews, Armenians, Arabs, Druze and Turks, and is characterized by recurrent self-limited febrile attacks of serosal inflammation involving the peritoneum, pleura and synovium [1]. The attacks may also involve the pericardium, skin, muscles and testes

[1–3]. Amyloidosis may develop in untreated patients [1]. FMF patients are treated with colchicine in a continuous dose of 1–2 mg/day. This drug prevents the febrile attacks in most patients and amyloidosis in almost all patients [4,5].

The FMF gene, which is mapped to chromosome 16p, was recently cloned and found to encode a previously unknown protein thought to be a transcription factor [6–8]. Although the role of the FMF gene in the development of FMF attacks is yet to be determined, its malfunction results eventually in inflammation with local and systemic consequences. During the febrile attacks, an acute-phase response develops, manifested by a marked increase in erythrocyte sedimentation rate, white blood cell count, fibrinogen, serum amyloid A, phospholipase A2, and C-reactive protein [1,9–11]. Inflammatory mediators like interleukin-6 and soluble receptors of tumor necrosis factor were recently found also to be increased during FMF attacks [10].

Systemic inflammation is an important factor in the initiation and development of atherosclerosis [12–15]. A recent study showed that in normal men, serum levels of CRP may predict future myocardial infarction and ischemic stroke. The increased risk of elevated CRP was independent of lipid-related and non-lipid related cardiovascular risk factors and was reduced by treatment with aspirin, causing a fall in baseline CRP levels [16]. With respect to the inflammatory background of atherosclerosis, one may expect an increased morbidity of IHD in patients with FMF. To examine this hypothesis, we designed a study to determine the prevalence of IHD in patients with FMF.

Patients and Methods

Patients

The registry of the Sheba Medical Center's FMF clinic consists of more than 5,000 patients. The files of the patients contain selected demographic and clinical data that are recorded at each patient visit. Of these patients, 290 consecutive colchicine-treated FMF patients over 40 years old who attended the FMF clinic during 1996 were asked to complete a questionnaire. The items in the questionnaire

IHD = ischemic heart disease
FMF = familial Mediterranean fever

CRP = C-reactive protein

related to: a) risk factors for IHD including smoking, overweight, diabetes mellitus, hypertension, sedentary lifestyle, family history of IHD in first-degree relatives; and b) manifestations indicating the presence of IHD.

Patients were considered to be obese if their weight was 30% higher than normal. The presence of diabetes mellitus and hypertension was accepted only if diagnosed by the patient's physician prior to the study. We had no systematic data on the lipid status of the patients, but no patient was known to suffer from, and none received therapy for, hyperlipidemia. All risk factors were accounted for only if present for at least 2 years. Patients were considered to suffer from IHD if they had a definite diagnosis or history of IHD prior to the study, including anginal syndrome, myocardial infarction, coronary artery bypass or findings of coronary artery disease on coronary catheterization, or if they had received treatment for IHD. Patients receiving corticosteroids or anti-inflammatory medications were excluded.

Controls

The same questionnaire and the same criteria were used for the two control groups. One group comprised the spouses of 233 FMF patients who completed the questionnaire either at the clinic (58%) or in a telephone interview; this group was chosen to serve as the normal population, exposed to similar environmental factors as the study group.

The second control group was a cohort of 126 consecutive patients, over age 40, with an inflammatory disease and attending one of the following outpatient clinics in our hospital: rheumatology, dermatology, ear/nose/throat, and ophthalmology. The systemic inflammatory conditions included rheumatoid and psoriatic arthritis treated with disease-modifying anti-rheumatic drugs only, uveitis, chronic otitis and different dermatoses. During the study period the patients were not in complete remission. All patients in this group completed the questionnaire. This group constituted the positive control group used to estimate the effect of chronic inflammatory process on the occurrence of IHD.

Control subjects treated with anti-inflammatory drugs such as colchicine, non-steroidal anti-inflammatory drugs or corticosteroids were excluded from the study. In addition, we compared our cohort of FMF patients with an age, gender and ethnically matched general population obtained from the reference data on IHD of the Israel Ministry of Health.

Statistical analysis

Chi-square tests were used to compare proportions of IHD, risk factors and demographic variables in patients and controls.

Results

The demographic data of the patients and controls are presented in Table 1. There was no significant difference between FMF patients and their spouses in age and gender,

Table 1. Demographic data in FMF patients and control groups

	N	Age (yr) (mean SD)	M:F
FMF patients	290	55.0 ± 8.8	143:147
Spouses	233	53.8 ± 10.0	104:129
Chronic inflammatory disease patients	126	58.8 ± 11.8*	61:65

* $P < 0.001$

Table 2. Prevalence (%) of risk factors and of IHD in FMF patients and control groups

	Smoking	Family history of IHD	Hyper-tension	Diabetes mellitus	Obesity	Sedentary lifestyle	IHD
FMF patients	36.6	28.6	27.9	11	10	70	15.5
Spouses	38.6	12.4*	17.2*	8.2	18.9*	92.7*	11.2
Chronic inflammatory disease patients	31.7	23.8	29.4	13.5	25.4*	77.8	30.2*

* $P < 0.05$, compared to FMF patients

Table 3. Prevalence (%) of risk factors in subjects with IHD

Risk factor	FMF (n = 45)		Spouses (n = 26)		Chronic inflammatory disease (n = 38)	
Smoking	49		54		37	
Family history	44		38		26	
Hypertension	49		42		50	
Diabetes	20		19		26	
Obesity	9		35		32	
Sedentary lifestyle	84		96		92	
No of risk factors	No.	%	No.	%	No.	%
6	0	0	0	0	1	2.6
5	2	4.4	3	11.5	2	5.3
4	6	13.3	6	23.1	3	7.9
3	15	33.3	6	23.1	15	39.5
2	14	31.3	6	23.1	12	31.6
1	8	17.8	5	19.2	3	7.9
0	0	0	0	0	2	5.3
Median no. of risk factors	2–3		2–3		2–3	

however there was a significant difference in age between FMF patients and other controls ($P < 0.001$).

Regarding risk factors for IHD, there was no significant difference between FMF patients and their spouses in the prevalence of smoking and of diabetes mellitus [Table 2]. However, compared with spouses, FMF patients had higher rates of hypertension and family history of IHD ($P < 0.05$) and lower rates of obesity and sedentary lifestyle ($P < 0.05$) [Table 2]. The prevalence of risk factors in the positive control group (patients with chronic inflammatory disease) was comparable to that of the FMF group in all items except for obesity, which was more common in the control group. Finally, IHD was similarly

prevalent among FMF patients and their spouses but was significantly less common ($P < 0.05$) in FMF as compared to the chronic inflammatory control patients [Table 2]. The prevalence of IHD in FMF patients was similar to that in the Israeli population (16%) of matched age and gender according to the population reference data of the Ministry of Health.

The prevalence of each of the various risk factors in subjects with IHD (45 FMF patients, 26 spouses and 38 chronic inflammatory disease patients) was comparable in the three groups of patients and controls except for a family history of IHD – which was significantly less common in FMF patients than in chronic inflammatory controls, and obesity – which was less common in FMF patients than in both control groups [Table 3]. However, the median number of risk factors for IHD per group – in all three groups of patients and controls – was similar.

Discussion

Inflammation was recently proven to be associated with the pathogenesis of atherosclerosis [12–20]. Since recurrent episodes of inflammation are the hallmark of FMF, we were interested to examine whether IHD is more common in FMF patients. We found that the frequency of IHD in colchicine-treated FMF patients was comparable to that of their spouses (representing the normal population) exposed to comparable environmental hazards, but was significantly lower than in untreated patients with other inflammatory conditions despite similar rates of risk factors [Tables 2 and 3]. In addition, when compared with the prevalence of IHD in a population matched for age, gender and ethnicity, as derived from reference data of the Israel Ministry of Health, FMF patients ranked within the expected range. These findings suggest that FMF patients are protected from the expected deleterious effects of inflammation on coronary arteries.

Attacks of FMF are associated with various markers of inflammation, which are reflected: a) clinically by fever and pain in the affected sites, b) histologically by an invasion of polymorphonuclear leukocytes to the serosal membranes, and c) serologically by activation of the cytokine cascade with elevated levels of IL-6 and soluble receptors of TNF, and particularly by the increased production of the acute-phase plasma proteins, fibrinogen, CRP, serum amyloid A and phospholipase A2 [1,9–11]. Given the nature of retrospective analysis, no systematic laboratory data were available for the present study.

Inflammation has a role in both the precipitation of acute ischemic events and the chronic development of atherosclerosis underlying IHD. This notion is supported by several lines of evidence. Elevated serum levels of CRP are predictive of future myocardial infarction and ischemic stroke, and administration of aspirin decreases this risk in direct correlation to the reduction in CRP values. Elevated levels of CRP were found

in patients with unstable angina [17] and are associated with a risk of fatal coronary disease among smokers [18]. In addition, inflammatory cell infiltrates and evidence for immunological activation of these cells may be found in atheromatous plaques in both acute and chronic ischemic syndromes [13–15]. IL-6 was found to be associated with the recruitment of macrophages and monocytes into atherosclerotic plaques [19]. And finally, patients in whom serum amyloid A increased significantly during the first 24 hours after percutaneous coronary angioplasty had a high relative risk for developing restenosis within a year after the procedure [20].

In view of the fact that inflammation is a risk factor for ischemic events and is a sine qua non of FMF attacks, and that colchicine prevents attacks completely in only 60% of FMF patients – with 30% experiencing a significant improvement but still suffering from some inflammatory FMF attacks, and the other 10% remaining unaffected – we expected an increased frequency of IHD in FMF patients, a hypothesis that was not confirmed in the present study. Failure to display higher than normal rates of IHD in FMF may still be attributed to the continuous lifelong therapy with colchicine, started in most FMF patients before age 20 [4,5]. This treatment probably reduced the expected increased frequency of IHD in our patients. The fact that fewer FMF patients were obese could also be related to colchicine therapy, which may reduce appetite and cause nausea and diarrhea [4], or was due simply to patients being more careful about what they eat in order to prevent abdominal attacks.

FMF is very common among the ethnically predisposed population. The frequency of the gene in carriers was computed to be 1:7–1:20 in North African Jews [21]. Such frequency favors a protecting role for the gene. However, in order to be widely scattered among the population, a protective gene should offer its benefits prior to or during the childbearing age. Protection against IHD, which is a disease of the elderly, does not carry any evolutionary advantage and therefore it is unlikely to be related to the FMF gene. Possible benefits of the FMF gene should be explored elsewhere. Similar conclusions that the FMF gene does not provide protection against IHD was obtained in another study [22]. The present analysis further supports a probable role for colchicine in the protection against inflammation induced by atherosclerosis.

In conclusion, colchicine-treated FMF patients in the present series, despite being subjected continuously to inflammation, a novel risk factor for IHD, sustained IHD with a frequency comparable to that in the general population. This finding was probably related to the favorable effect of colchicine.

References

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967;43:227–53.

IL = interleukin

TNF = tumor necrosis factor

2. Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A. Attacks of pericarditis as a manifestation of familial Mediterranean fever. *Q J Med* 1997;90:643–7.

3. Livneh A, Langevitz P, Zemer D, Migdal A, Sohar E, Pras M. The changing face of familial Mediterranean fever. *Semin Arthritis Rheum* 1996;26:612–27.

4. Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, Gafni J. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. *N Engl J Med* 1974;291:932–4.

5. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986;314:1001–5.

6. Pras E, Aksentijevich I, Gruberg L, Prosen L, Dean M, Pras M, Kastner DL. Mapping of a gene causing familial Mediterranean fever to the short arm of chromosome 16. *N Engl J Med* 1992;326:1509–13.

7. The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997;90:797–807.

8. The French FMF Consortium. A candidate gene for familial Mediterranean fever. *Nat Genet* 1997;17:25–31.

9. Knecht A, de Beer FC, Pras M. Serum amyloid A protein in familial Mediterranean fever. *Ann Intern Med* 1985;102:71–2.

10. Gang N, Drenth YPH, Livneh A, Langevitz P, Zemer D, Brezniak N, Pras M, van der Meer YWM. Activation of the cytokine network in familial Mediterranean fever. *J Rheumatol* 1999;26(4):890–7

11. Cang J, Musser JH, McGregor H. Phospholipase A2: function and pharmacological regulation. *Biochem Pharmacol* 1987;36:2429–36.

12. Munro JM, Cotran RS. The pathogenesis of atherosclerosis: atherogenesis and inflammation. *Lab Invest* 1988;58:249–61.

13. Fuster V, Badimon L, Badimon JJ, Chesebro YM. The pathogenesis of coronary artery disease and of the acute coronary symptoms. *N Engl J Med* 1992;326:242–50.

14. Ross R. The pathogenesis of artherosclerosis: a prospective for the 1990s. *Nature* 1993;362:801–9.

15. Alexander RW. Inflammation and coronary artery disease. *N Engl J Med* 1994;331:468–9.

16. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973–9.

17. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994;331:417–24.

18. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary artery disease in the MRFIT nested case-control study. *Am J Epidemiol* 1996;14:537–47.

19. Biasucci LM, Viterlli A, Liuzzo G, Almatura S, Caligiuri G, Monaco C, Rebuzzi AG, Gilibero G, Maseri A. Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996;94:874–7.

20. Blum A, Vardinon N, Kaplan G, Laniado S, Yust I, Burk M, Miller H. Autoimmune and inflammatory responses may have an additive effect in postpercutaneous transluminal coronary angioplasty restenosis. *Am J Cardiol* 1988;81:339–41.

21. Daniels M, Shohat T, Brenner-Ullman A. Familial Mediterranean fever. High gene frequency among the non-Ashkenazic and Ashkenazic Jewish population in Israel. *Am J Med Genet* 1995;55:311–14.

22. Brenner-Ullman A, Melzer-Ofir H, Daniels M, Shohat M. Possible protection against asthma in heterozygotes for familial Mediterranean fever. *Am J Med Genet* 1994;53:172–5.

Correspondence: Dr. P. Langevitz, Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer 52621, Israel. Phone: (972-3) 530-2454/931-4458, Fax: (972-3) 530-2114/530-7002.