Carriage of Mediterranean Fever (*MEFV*) Mutations in Patients with Postpericardiotomy Syndrome (PPS)

Ido-David Dechtman MD[1,4]*, Chagai Grossman MD[1,4]*, Yael Shinar MD[2,4] Rinat Cohen MD[2,4], Eyal Nachum MD[3,4], Ehud Raanani MD[3,4], Avi Livneh MD[1,4] and Ilan Ben-Zvi MD[1,4]

[1]Department of Internal Medicine F, [2]Heller Institute of Medical Research and [3]Department of Cardiac Surgery, Sheba Medical Center, Tel Hashomer, Israel
[4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Postpericardiotomy syndrome (PPS) is characterized by pleuro-pericardial inflammation, which occurs in patients undergoing surgical procedures involving the pleura, pericardium, or both. The syndrome is considered to be immune mediated. However, its pathogenesis is not fully understood. It has previously been demonstrated that the Mediterranean Fever (*MEFV*) gene, which is associated with familial Mediterranean fever (FMF), has a role in the activation and expression of several inflammatory diseases.

Objectives: To investigate whether carriage of the *MEFV* mutation may precipitate PPS or affect its phenotype.

Methods: The study population included 45 patients who underwent cardiac surgery and developed PPS. The control group was comprised of 41 patients who did not develop PPS. Clinical and demographic data was collected. The severity of PPS was evaluated. Genetic analysis to determine the carriage of one the three most common *MEFV* gene mutations (M694V, V726A, E148Q) was performed. The carriage rate of *MEFV* mutations in patients with and without PPS was compared. Association between *MEFV* mutation carriage and severity of PPS was evaluated.

Results: The rate of mutation carriage in the *MEFV* gene was similar in patients with and without PPS (15.6% in the study groups vs. 29.3% in the control group, $P = 0.1937$). The rate of mutation carriage in the *MEFV* gene was significantly lower among patients with severe PPS as compared to patients with mild-moderate PPS (4.8% vs. 25%, $P < 0.05$).

Conclusions: Carriage of mutations in the *MEFV* gene is not associated with development of PPS; however, it may affect PPS severity.

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KEY WORDS: Mediterranean FeVer (*MEFV*) gene mutations, familial Mediterranean fever (FMF), ethnic origin, postpericardiotomy syndrome (PPS)

Postpericardiotomy syndrome (PPS) is characterized by pleuro-pericardial inflammation, which occurs in 10–40%, of patients undergoing surgical procedures involving the pleura, pericardium, or both. The syndrome occurs more frequently following cardiac surgeries [1], yet its pathogenesis is not fully understood. Evidence supports the involvement of the immune system in PPS. It seems to be initiated by the combination of damage to mesothelial pericardial cells and blood in the pericardial space. The initial injury is thought to release cardiac antigens and stimulate an immune response. The immune complexes that are generated are then deposited in the pericardium, pleura, and lungs, which elicits an inflammatory response [2]. Studies in patients undergoing cardiac surgery have found a statistically significant correlation between the postoperative and preoperative ratios of antiactin and antimyosin antibodies and the clinical occurrence of post-cardiac injury [3]. Several clinical observations also support immune activation in PPS:

- Prolonged latent period from cardiac injury to the clinical onset of post-cardiac injury syndrome
- Excellent response to anti-inflammatory therapy and occasional relapses after steroid withdrawal [2]
- Lack of viral or bacterial agents in the pericardial fluid

The gene associated with familial Mediterranean fever (FMF) was discovered in 1997 and named Mediterranean Fever (*MEFV*) [4].The gene is located on the short arm of chromosome 6. It encodes a 781 amino acid protein called pyrin that is expressed predominantly in the cytoplasm of myeloid cells along with synovial fibroblasts and dendritic cells. Pyrin appears to act as an intra-nuclear regulator of transcription of the peptides involved in inflammation [4-6], mainly the innate immune system, which constitutes a primary defense against external pathogens and other noxious agents. Pyrin was shown to be a major regulatory component of the inflammasome, a complex of proteins that, when activated, trigger the release of interleukin-1 beta (IL1β) and are mediators of apoptosis [7,8].

The typical manifestations of FMF are recurrent attacks of serositis accompanied by high fever [9]. Patients with FMF have been found to have a higher incidence of several other

*The first and second authors contributed equally to this study

inflammatory diseases, including polyarteritis nodosa, Henoch Schonlein purpura, and Behçet's disease [10-12].The *MEFV* gene was also shown to have an important role in the expression and phenotype of several other inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE) [13-24]. In view of the extensive effect of mutations in the *MEFV* gene on inflammatory diseases, we aimed to investigate whether there is an association between the incidence of PPS and its severity and *MEFV* mutations.

PATIENTS AND METHODS

The study population consisted of patients who underwent cardiac surgery between the years 2008–2014 at the Sheba Medical Center in Israel and were diagnosed with PPS during the initial hospitalization or in a following hospitalization. The control group consisted of patients who underwent cardiac surgery and did not develop PPS for 3 months following the surgery. The study was approved by the institutional review board of our institution and all participants in the study signed an informed consent. The patients in the study population completed a comprehensive questionnaire about their demographic and clinical data and the severity of their PPS. Blood samples were taken to determine the carriage of one of the three most common *MEFV* gene mutations (M694V, V726A, and E148Q). Genetic analysis was performed using standard laboratory methods, including DNA extraction and amplification of DNA specific regions by polumerase chain reaction analysis [25].

STATISTICAL ANALYSIS

Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the Fisher exact test. All statistical tests were two-tailed. A value of $P < 0.05$ was considered to be statistically significant. Z-test was used to evaluate the association between carriage of each *MEFV* mutations and severity of PPS (severe vs. mild-moderate). One tailed chi-square test was used to evaluate the association between carriage of any of the three most common mutations and severity of PPS.

RESULTS

The study and control groups consisted of 45 and 41 patients, respectively. Two additional patients were retrospectively excluded because they were eventually diagnosed with postoperative infection and not PPS. Baseline clinical and demographic features of the patients are presented in Table 1. The rate of female gender was significantly higher in patients with PPS as compared to patients without PPS. Patient age, living area, type of operation, and ethnic origin were similar in the groups.

The carriage rate of *MEFV* gene mutations in the control group was 29.3% compared to 15.6% in the study group [Table 1]. All the patients who were found to be carriers of the *MEFV* mutation were heterozygotes. The carriage rate of mutations in the *MEFV* gene according to ethnic origin (Ashkenazi vs. non-Ashkenazi Jews) is presented in Table 2. There were no significant differences in the carriage rate of mutations in the *MEFV* gene between the groups. The carriage rate of any *MEFV* mutation according to PPS severity is presented in Table 3.

Table 1. Clinical and demographic features of the study population

Variable		PPS (N=45)	Control (N=41)	*P* value
Male gender, n (%)		8 (17.7)	24 (58)	0.0001
Average age (years)		63.7	63.04	0.50926
Type of operation, n (%)	CABG	21 (46.6)	13 (31.7)	0.1886
	Aortic valve	7 (15.5)	10 (24.4)	0.4174
	Mitral valve	5 (11.1)	9 (22)	0.2438
	Aortic + mitral valve	4 (8.9)	2 (4.9)	0.6783
	CABG + valvular	5 (11.1)	9 (22)	1
	Ather	3 (6.7)	2 (4.9)	1
Severity of PPS	Mild (1–3)	0	N/A	
	Moderate (4–7)	24 (53.3)		
	Severe (7–9)	21 (46.7)		
Ethnic origin, n (%)	Jewish Ashkenazi	25 (55.5)	24 (58.5)	0.8297
	Jewish non-Ashkenazi	16 (35.5)	12 (29.3)	0.6463
	Druze	1 (2.2)	0	1
	Muslim	2 (4.4)	3 (7.3)	0.6659
	Other	1 (2.2)	2 (4.9)	0.6034
MEFV mutation, n (%)	M694V	0	3 (7.3)	0.1042
	V726A	4 (8.9)	5 (12.2)	0.7309
	E148Q	3 (6.7)	4 (9.8)	0.7044
	Any mutation*	7 (15.6)	12 (29.3)	0.1927

MEFV = Mediterranean fever gene, PPS = postpericardiotomy syndrome, CABG = coronary artery bypass graft, N/A = not applicable

*refers to any of the three mutations (M694V, V726A, E148Q)

Table 2. Carriage rate of *MEFV* mutations according to ethnic origin (Ashkenazi vs. non-Ashkenazi Jews)

	Mutation	Ashkenazi Jews, n (%)	Non-Ashkenazi Jews, n (%)	*P* value
PPS	M694V, n (%)	0	0	
	V726A, n (%)	4 (16)	0	0.1174
	E148Q, n (%)	0	3 (15)	0.0803
	Any mutation *	4 (16)	3 (15)	1
Control group	M694V, n (%)	0	3 (17.6)	0.0638
	V726A, n (%)	3 (12.5)	2 (11.8)	1
	E148Q, n (%)	2 (8.3)	2 (11.8)	1
	Any mutation*	5 (20.8)	7 (41.2)	0.1838

MEFV = Mediterranean fever gene, PPS = postpericardiotomy syndrome

*refers to any of the three mutations (M694V, V726A, E148Q)

Patients with severe disease had a significantly lower carriage rate of *MEFV* mutation compared to patients with mild to moderate disease (4.8% vs. 25%, $P < 0.05$).

The carriage rate of specific *MEFV* gene mutations in the study group, according to the severity of PPS and compared to the control group, is presented in Table 4. The carriage rate of any *MEFV* mutation was significantly higher in participants who did not develop PPS compare to patients who developed severe PPS (29.3% vs. 4.8%, $P < 0.05$).

DISCUSSION

We found that the carriage rate of *MEFV* mutations in patients who developed PPS following cardiac surgery to be similar to patients who did not develop PPS. Unexpectedly, we found a significantly higher carriage rate of *MEFV* mutations in patients who did not develop PPS compared to patients who developed severe PPS, and a significantly lower carriage rate of *MEFV* mutations in patients with severe PPS as compared to patients with mild-moderate PPS. This difference may indicate that carriage of *MEFV* mutations may have some protective effect against developing severe PPS. Several studies demonstrated an association between carriage of *MEFV* mutations and the severity of several autoimmune and auto-inflammatory diseases. In most cases, mutations in the *MEFV* gene are associated with a more severe disease [12-22], but in some cases they are associated with a milder phenotype [23-24]. Livneh and colleagues demonstrated that *MEFV* appears to be a susceptibility and modifier gene in Behçet's disease [12-14]. Fidder et al. [17,18] demonstrated that Crohn's disease appears to be more prevalent in patients with FMF and that presence of *MEFV* mutations is associated with a stricturing disease and extra-intestinal manifestations. Mutations in the *MEFV* gene, and particularly the E148Q mutation, have been found to be an independent modifier of the clinical manifestations of rheumatoid arthritis, as patients carrying the mutation had a higher mean severity score than non-carriers [19]. Several studies have shown that patients with multiple sclerosis (MS) carrying *MEFV* mutations seem to have a susceptibility to develop a more progressive disease. Moreover, *MEFV* mutations may increase the risk of MS development [20-22]. According to the results of our study it seems that carriage of *MEFV* mutations may have a protective role in patients with PPS. Carriage of *MEFV* mutations was not associated with a lower incidence of PPS, but was associated with lower severity scores of the disease. The beneficial effect of carriage of *MEFV* mutations was also shown in SLE, where it was shown to contribute to an excess of inflammatory manifestations such as fever and pleuritis, while thwarting more severe renal manifestations [23]. Rabinovitch and associates [24] found that *MEFV* mutations have a protective role in the pathogenesis of asthma, as patients with asthma were found to have a significantly lower mutation carrier rate than ethnically matched healthy individuals. In addition, carriers of *MEFV* mutations had less severe disease than non-carriers. The mechanism responsible for the effect of *MEFV* mutations on diseases other than FMF is not fully understood.

Several possible mechanisms that may explain the protective role of *MEFV* mutation carriage were proposed. One of the proposed mechanisms offered relates to the elevation of the inflammatory markers C-reactive protein and serum amyloid P in patients carrying *MEFV* mutations. These proteins serve a role in removal of autoantigens and by-products of apoptosis, and thus may have a protective role in renal damage, which is immune mediated, in SLE [23]. Another possible mechanism proposed is that wild-type pyrin, which is mainly expressed in white blood cells, may divert the balance between inflammation and apoptosis toward the latter, counteracting the T helper 2 mediated reduced apoptosis of inflammatory cells, or suppression through interferon-γ of propagation of inflammation mediated by T helper 2 activity [24].

Table 3. Carriage rate of *MEFV* mutations according to PPS severity

	Mild-moderate PPS	Severe PPS	Total
Carriage of *MEFV* mutation, n (%)*	6 (25)	1 (4.8)	7 (15.6)
No *MEFV* mutations, n (%)*	18 (75)	20 (95.2)	38 (84.4)
Total	24	21	45

MEFV = Mediterranean fever gene, PPS = postpericardiotomy syndrome
*refers to any of the three mutations (M694V, V726A, E148Q)

Table 4. Carriage rate of *MEFV* mutations according to severity of PPS and compared to control group

Mutation	Mild-moderate PPS (N=6)	Severe PPS (N=1)	Control group
M694V, n (%)	0	0	3 (7.3)
V72, n (%)	4 (16.7)	0	5 (12.5)
E148Q, n (%)	2 (8.3)	1 (4.8)	4 (9.8)
Any mutation*	6 (25)	1 (4.8)	12 (29.3)

MEFV = Mediterranean fever gene, PPS = postpericardiotomy syndrome
*refers to any of the three mutations (M694V, V726A, E148Q)

STUDY LIMITATIONS

Our study has several limitations. They include.

- Diagnosis of PPS is based on clinical grounds, yet it does not have validated diagnostic criteria
- We analyzed only three known mutations in the *MEFV* gene. Moreover, it is possible that besides mutations in the *MEFV* gene, there are other mutations associated with auto-inflammatory disease that were not investigated in the present study, such as cryopirin-associated periodic syndromes and tumor necrosis factor associated periodic syndrome, which may also modify the incidence and severity of PPS. Nevertheless, the mutations investigated in our study are

the most widely distributed, and therefore best represent the genetic spectrum of FMF

- There is no conventional severity index scale for PPS. In this study, we used clinical and laboratory measures to assess disease severity, but this severity index is not universal

CONCLUSIONS

In conclusion, in this study we did not find an association between *MEFV* mutations carriage and incidence of PPS. However, *MEFV* mutations carriage had a protective role in the development of severe PPS. Further studies are needed to confirm the findings of this study.

Correspondence
Dr. C. Grossman
Dept. of Internal Medicine F and Rheumatology Unit, Sheba Medical Center, Tel Hashomer 5265601, Israel
Fax: (972-77) 560-7197
email: chagaigr@gmail.com

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Capsule

Differentiating myeloid cells

Hematopoietic stem cells are a common progenitor of adaptive and innate immune cells. However, the precise factors that guide differentiation down these disparate pathways remain unclear, in part because of difficulties in working with small numbers of precursor cells. Lee and colleagues solved this problem for myeloid lineage cells by immortalizing murine myeloid progenitors with conditionally over-expressed Hoxb8 and labeling these cells with a Ccr2/ Cx_3cr1 dual reporter. They found through a small-molecule library screen and confirmatory in vivo validation that the mTORC1-S6K1-Myc pathway regulates myeloid differentiation. Disrupting this pathway in progenitor cells results in a lack of monocytes and neutrophils. Hence, the mTORC1-S6K1-Myc pathway functions as a checkpoint in terminal myeloid differentiation.

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Eitan Israel

"When you re-read a classic, you do not see more in the book than you did before; you see more in yourself than there was before"

Clifton Fadiman, (1904–1999), American intellectual, author, editor, radio and television personality