

*Cardiac Changes and Evaluation in patients
with familial Mediterranean fever
and the role of MEFV gene mutations*

Thesis

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By

Dr. Lubna Mohamed Abd El Rahman
(M.B.B.Ch-M.Sc.)

Under Supervision of

Prof. Dr. Samia Salah El-Dein Mahmoud

Professor of Pediatric Faculty of
Medicine - Cairo University

Assist. Prof. Rasha Ibrahim Ammar

Assist Professor of Pediatric Faculty of
Medicine - Cairo University

Prof. Dr. Hala Fathi Shaybah El-Hamed

Professor of Clinical Pathology Faculty of
Medicine - Cairo University

Assist. Prof. Dr. Rania Ali Hegazy

Assist Professor of Pediatric Faculty of
Medicine - Cairo University

*Faculty of Medicine
Cairo University*

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LIST OF ABBREVIATIONS

\$	Syndrome
A	Peak Flow velocity in late diastole
AA	Amyloid Associated protein
ACC	American College of Cardiology
AHA	American Heart Association
AL	Amyloid Light chain protein
Am	Peak Flow velocity in early systole quad with a square body in mitral
ANOVA	Analysis Of Values
Ao	Aorta
ARMS	Amplification refractory mutation system
AS	Acute sacroiliitis
ASBO	Adhesive small bowel obstruction
ASC	Apoptosis associated speck-like protein
ASD	Atrial septal defect
BASRI	Bath Ankylosing spondylitis Radiology Index scores
BMI	Body Mass Index
C	Complement
C 3	Complement 3
C5a	Complement 5a
CAPS	Cryopyrin associated periodic syndrome
CARD	Caspase recruitment domain
CC	Chemokines
CD	Cluster Differentiation
CD	Crohns Disease
CD2BP1	CD2 binding protein 1
CDNA	Complementary deoxyribonucleic acid
CFR	Coronary Flow Reserve
CHD	Congenital heart disease
CIAS	Cold induced autoinflammatory syndrome
CINCA	Chronic infantile neurologic cutaneous and articular
CLR1.1	Caterpillar-like receptor 1.1
CRP	C - Reactive Protein
CUSPH	Cairo University Specialized Pediatric Hospital
CW	Continuous Wave Doppler

DNA	Deoxyribonucleic acid
E	Peak Flow velocity in early diastole
EB	Endomyocardial Biopsy
EC	Echo Cardiology
ECG	Electro - Cardio gram
EDTA	Ethylene diamine tetra acetic acid
Em	Peak Flow velocity in early diastole quad with a square body in mitral
ERO	Effective regurgitate orifice
ESR	Erythrocyte Sedimentation Rate
FCAS	Familial cold autsinflammatory syndrome
FCUS	Familial cold urticaria syndrome
FDA	Food and Drug Administration
FH	Family history
FHF	Familial Hibernian fever
FMF	Familial Mediterranean fever
FS	Fraction shortening
GFR	Glomerular filtration rate V
h	hour
Ha	Hour angle
Hb	Hemoglobin
HCU	Hand Carrier cardiac Ultrasound
Hi PRF	High Pulse Repition Doppler
HIDS	Hyper immunoglobulinemia D syndrome
HLA	Human Leucocytic Antigen
HRQOL	Health related quality of life
HRV	Heart Rate Variability
HSP	Henoch- schonleinpurpura
IBD	Inflammatory bowl disease
IFN	Interferon
Ig	Immunoglobulin
IHD	Ischemic HeartDisease
IL	Interleukin
IL-IR a	Interleukin IR a
IRAP	Idiopathic Recurrent Acute Pericarditis
IV S	Inter ventricular septum
JIA	Juvenile Idiopathic Arthritis
Kg	Kilogram

KIR	Killer cell immunoglobulin-like receptors
LA	Left atrium
LL	Lower Limb
LPA	Left pulmonary artery
LPIN2	Lipinpronet protein and cluster in human of interpro domains family
LRR	Leucine –rich repeat
LV	Left Ventricle
LVEDD	Left ventricular end diastolic diameter
LVESD	Left ventricular end systolic diameter
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVPW	Left ventricular post wall
MDP	Metal Dependent Phosphohydrolasescintigraphy
MEFV	Mediterranean FeVer
MIP	Macrophage inflammatory protein
MKD	Mevalonate kinase deficiency
MPA	main pulmonary artery
MPI	Myocardial performance Index
MRI	Magnetic Resonance Imaging
MVK	Mevalonate kinase
MWS	Mukle - Wells syndrome
NALP3	NACHT(nucleotide binding), LRR and PYD domain containing protein 3
NBS	Nucleoide –binding site
Neut	Neutrophil
NK	Natural killer
NLRP3	Nod-like receptor family pyrin domain containing 3
no	number
NO	Nitric Oxide
NOD2	Nucleotide binding oligomerization domain containing 2
NOMID	Neonatal onset multisystem inflammatory disease
NSAIDs	Non - steroidal anti - inflammatory
OMIM	Online Mendelian inheritance in man
PAMP	Pathogen-associated molecular pattern
PAN	Poly Arthritis Nodosa
PAPA	Pyogenic sterile arthritis, pyodermagangrenosum and acne
PCIS	Post Cardiac Injury Syndrome
PCR	Polymerase chain reaction

Pd	P-wave dispersion
PDA	Patent ductus arteriosus
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
PG	Pyodermagangrenosum
PSTPIP1	Proline serine theonine phosphatase interacting protein 1
PW	Pulsed Wave Doppler
Py D	Pyrin Domain
RHD	Rheumatic Heart Disease
RPA	Right pulmonary artery
RV	Right ventricle
SAA 1	Serum amyloid A1
SD	Standard deviation
SNPs	Single nucleotide polymorphism
SNSA	Sero-negative spondyloarthropathy
SPRY	Surname of gene domain
SV	Stroke volume
T NFRSF 1A	Tumor necrosis factor receptor superfamily 1A
T NF-α	Tumor necrosis factor alpha
TDE	Tissue Doppler Echocardiography
TDI	Tissue Doppler Imaging
TEE	Trans Esophageal Echocardiography
TLC	Total Leucocytic Count
TNF	Tumor necrosis factor
TRAPS	Tumor necrosis factor receptor – associated periodic syndrome
TTE	Transthoracic Echocardiography
U.PTN	Urinary protein
UC	Ulcerative Colitis
USA	United States of America
UTR	Un translated region coding sequence
VHDs	Valvular heart diseases
VNTR	Variable number Tandem repeats polymorphism
VSD	Ventricular septal defect
WBC	White blood cell count
Yrs	Years

Abstract

Our study include 108 patients suffering of familial Mediterranean fever, randomly selected between patients of rheumatology clinic in children specialized hospital, for cardiac evaluation and affections, and its relation with gene mutation. Screening was done in 12 stes genes for studding the correlation of clinical presentation and its relation to phenotype-genotype gene mutation correlation, we found that 50% of positive gene mutation have cardiac affection.

Key words: Familial Mediterranean Fever - Cardiac diseases -
Gene mutation.

Introduction and Aim of the work

Introduction :

World wide familial Mediterranean fever FMF is the most common auto-inflammatory disorder (*Ozen et al.,2009*). Familial Mediterranean fever (FMF) is a genetic disorder inherited as an autosomal recessive disease (*Caliskan et al.,2007*). It is characterized by recurrent inflammatory febrile attacks of serosal and synovial membranes and predominately affects the populations arising from the Mediterranean basin (*Baysal et al.,2009*). It manifests by recurrent attacks of peritonitis, pleuritis, pericarditis, synovitis, arthritis, and fever(*Taviletal.,2008*).

MEFV gene mutations are responsible for the disease and its protein product, pyrin or marenostrin, plays an essential role in the regulation of the inflammatory reactions. MEFV gene contains 10 exons and most of the mutations have been found on the last exon. Up to date 152 mutations and polymorphisms have been reported (*Aysen et al.,2009*).

In contrary to other rheumatological disorders, there have been a limited number of studies investigating the cardiac involvement in patients with FMF (*Tavil et al.,2008*), although the disease may carry a potential for cardiovascular disorders because of sustained inflammation during its course (*Koklu etal.,2005*).

The presence of inflammation during the attack-free periods of FMF have been shown in many studies (*Kanbayet al.,2009*).

The spectrum of cardiac involvement in children with FMF has not been well studied. Impairment of diastolic function parameters (*Baysal et al.,2009*), pericarditis and pericardial effusion (*Terekeci et al.,2008*), atrial mechanical delay and increased *P* wave dispersion (*Acar et al.,2009*), and impaired coronary microvascular function (*Caliskan et al 2007*) have all been reported in various studies.

Aim of Work:

The degree of cardiac involvement in children with FMF is not well studied. Associations between cardiac affections and MEFV gene mutations have not been reported.

The present work aims at defining the frequency and spectrum of cardiac affection in Egyptian children with FMF. The role of MEFV gene mutations in determining presence of cardiac involvement will be investigated, and to examine the correlation of the genotype and phenotype of mutations that will be found.

FAMILIAL MEDITERRANEAN FEVER

Definition:

Familial Mediterranean fever (FMF) is the most common of the autoinflammatory syndromes, and is most frequent periodic fever syndrome, it is an autosomal recessive disorder (*Kanbayetal, 2009*). FMF is characterized by recurrent inflammatory attacks of fever and serositis. It occurs with high frequency in certain population in Mediterranean area (*Bakkaloglu et al, 2003*).

Disease characteristics. Familial Mediterranean fever (FMF) comprises two phenotypes: type 1 and type 2. FMF type 1 is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis. The symptoms and severity vary among affected individuals, sometimes even among members of the same family. Amyloidosis, which can lead to renal failure, is the most severe complication. FMF type 2 is characterized by amyloidosis as the first clinical manifestation of FMF in an otherwise asymptomatic individual. (*Gabrielle, et al, 2009*)

Pyrin or marenostrin Plays an essential role in the regulation of the inflammatory reactions. (*Aysen et al, 2009*).

The disease course can be complicated by development of amyloid depositions and organ failure which can be fatal (*Medlej et al, 2004*).

Worldwide, it has been suggested that environmental factors affect the phenotype as some patients do not develop the complication of secondary amyloidosis. (*ozen et al, 2009*).

Rationale (Historical Background):

Mediterranean Fever was identified two decades ago; however, only recent studies have shed light on its pathogenesis. This focuses on recent studies that have led us to more fully understand FMF pathogenesis (*Kanbay et al, 2009*).

Janeway and Mosenthal in 1908 were the first to report what they termed "unusual paroxysmal" followed by Siegal in 1945 who reported additional 5 cases of "benign paroxysmal peritonitis" and suggested that FMF is a distinct clinical entity. The name "periodic disease" was used by Reimann in 1951. (*Eliakim et al, 1996*).

Linch in 1974 used the term "familial Mediterranean fever" , and gave detailed descriptions of this clinical entity. Another term "recurrent polyserositis" was used in 1961 to describe the disease by Ehrenfeld and Eliakim. The effect of Colchicine on the symptoms was reported by Goldfmgger in 1972 and Eliakim and Linch in 1973 (*Mijatovic et al, 2003*).

Although FMF primarily affects populations living around Mediterranean-basin (Jewish, Armenian, North African, Arab and Turkish populations), it is also a worldwide disease due to widespread inter-continental travel in twentieth century (*Touito et al, 2007*).

FMF is strongly familial and inheritance is autosomal *recessive* (*Ben-Chetrit, et al 2001*). Estimates of carrier frequency in Mediterranean population range from 1 in 5 to 1 in 16 (*Daniels et al, 1995*).

The actual incidence in families with healthy parents has been reported to be 18%, and that in families with one affected parent 30% (*Shohat et al, 1992*).

Epidemiology :

El Gezery and Abou-Zeid in 2010 were able to identify a wide spectrum of MEFV mutations in Egyptian patients in whom FMF was diagnosed. Frequencies of individual mutations showed some differences from those in other Mediterranean populations. (*El Gezery et al., 2010*)

Consanguinity is not the only factor influencing the occurrence of autosomal recessive disorders such as familial Mediterranean fever (FMF). The extended multiple consanguineous study demonstrates that the population frequency of certain mutations (so-called "ancient" mutations) can be at least equally important. In high-risk populations different combinations of mutations can occur within the same family, increasing not only the intrafamilial clinical variability, but also causing considerable recurrence risks even in marriages with unrelated spouses. (*Seidel et al, 2009*).

Genotypic profiles of the natural killer cell immunoglobulin-like receptors (KIR) which are DNA typed gene and pseudogene loci have been reported to vary among different ethnic groups and variable clinical entities. (*Mahfouz et al, 2009*).