Hematological Changes in Children with Familial Mediterranean fever

Thesis

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ABSTRACT

Familial Mediterranean Fever (FMF), is an autosomal recessive disease that affects commonly Mediterranean populations. The aim of the present study was not only to review clinical and demographic features of child-onset Familial Mediterranean Fever (FMF) patients but also to investigate Hematological changes that could occur in a cohort of 100 FMF patients randomly selected from Rheumatology clinic at Specialized Cairo University Pediatric Hospital. Hematological parameters as Hgb, Hct, MCV, TLC, PLT count were retrospectively reviewed to all patients at time of diagnosis and after colchicine therapy. Our results recorded a significant elevation of both Hgb and Hct levels after a period of colchicine therapy, we also had 58 patients (58%) suffered anemia regarding their ages at time of diagnosis, of those 52 patients (89%) had their anemia improved with therapy, regarding the TLC there was no significant change in the count before and after treatment with colchicine but we noticed having 4 patients presenting with absolute neutropenia at time of diagnosis, their neutrophil count was elevated after therapy, only one patient presented with leucocytosis at time of diagnosis, his TLC dropped after a period of therapy, we did not find a significant change in the platelet count before and after treatment. In conclusion our data suggests that colchicine use was effective in controlling the attacks and also in improving both Hgb and Hct levels of the patients.

Key words: Familial Mediterranean Fever, Anemia, Colchicine

List of Abbreviations

AA	:	Amyloid A
ACD	:	Anemia of Chronic Disease
AID	:	Anemia of inflammatory Disease
AML	:	Acute Myelogenous Leukemia
APR	:	Acute phase response
C	:	Complement
CAPS		Cryopyrin associated periodic syndrome
CARD15/ NOD2	:	Caspase activating recruitment domain 15/ nucleotide-binding oligomerisation domain protein 2
CBC	:	Complete Blood Count
CD4	:	Cluster of Differentiation 4
CD69	:	Cluster of Differentiation 69
CDA	:	Chronic disease anemia
CHD	:	Coronary Heart Disease
CIAS	:	Cold induced auto inflammatory syndrome
CINCA	:	Chronic infantile neurologic cutaneous and articular
CRP	:	C- reactive protein
DNA	:	Deoxyribonucleic acid
ELA2	:	Mutations in the human neutrophil elastase gene
EPO	:	Erythropoietin
ESR	:	Erythrocyte sedimentation rate
F	:	Female
FMF	:	Familial Mediterranean fever
Hgb	:	Hemoglobin
HIDS	:	Hyper immunoglobulinemia D syndrome
IDA	:	Iron Deficiency Anemia
IFN	:	Interferon
Ig	:	Immunoglobulin
IL	:	Interleukin
JRA	:	Juvenile Rheumatoid Arthritis
LTB4	:	Leukotriene B4
M	:	Male

MCV	:	Mean Corpuscular Volume
MDS	:	Myelodysplasia
MEFV	:	Mediterranean Fever
MIF	:	Macrophage migration inhibiting factor
MPV	:	Mean platelet volume
Mtor	:	Mammalian target of rapamycin
MVK	:	Mevalonate kinase
NK	:	Natural killer
NSAID	:	Non- steroidal anti-inflammatory drugs
PBMCS	:	Peripheral blood mononuclear cells
PFAPA	:	Periodic fever, , aphthous stomatitis, pharyngitis and cervical adenitis
PLT	:	Platelet
RO52	:	Ro proteins, a protein of 52 kD
SAA1	:	Serum amyloid A1
SD	:	Standard deviation
SE	:	Standard error
SEG	:	Segmented
SF	:	Serum ferittin
SICAM	:	Soluble intracellular adhesion molecule
SLE	:	Systemic Lupus Erythematosis
ST	:	Staph
STFR	:	Serum Transferrin
TH1	:	T Helper 1
TLC	:	Total Leukocytic count
TNF	:	Tumor necrosis factor
TNF-α	:	Tumor necrosis factor alpha
TRAPS	:	Tumor necrosis factor receptor –associated periodic syndrome
VEGFr	:	Vascular endothelial growth factor receptor.
Yrs	:	Years

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INTRODUCTION

Familial Mediterranean Fever (FMF), is an autosomal recessive disease that affects commonly populations of Armenian, Arab, Sephardic Jewish or Turkish origin and it is not uncommon in other Mediterranean populations, such as Italians, Spanish, Portuguese, French, and Greeks. The historic trace-back of the shared haplotype and common mutations suggests a common ancestor at least 2000 years ago, when most of these populations were living together in the eastern Mediterranean basin ***(Kastner and Aksentijevich, 2005).***

Although an unexplained clinical heterogeneity is not uncommon, the diagnosis of the disease, which is based on various sets of clinical criteria**,** can be confirmed by molecular means that provides the only objective diagnostic criterion. ***(Livneh et al., 1997)***.

In 1997 the gene linked to FMF, called MEFV, was cloned from chromosome 16p using positional cloning and some of the mutations associated with the disease were identified ***(Ben-Chetrit et al., 1998).***

The gene comprises 10 exons, spanning approximately 15 kb of genomic DNA and encodes a 781 amino acid-long protein. All four of the initial FMF-associated mutations in MEFV were in exon 10, and even now, with over 166 mutations having been identified ***(Milhavet et al., 2008).***

Livneh et al. (1997) referres to that exon 10 remains the major site of mutations with a smaller cluster in exon 2.

Nearly all of the known FMF-associated mutations encode conservative missense changes. The most frequent mutations (M680I, M694V, V726A, M694I and E148Q) are found in more than two thirds of cases ***(Yilmaz et al., 2003).***

The incomplete penetrance and the varying expression of FMF suggest the presence of other, possibly genetic, factors that could influence the expression of illness (***Medlej-Hashim et al., 2005***).

Colchicine is the preferred drug for FMF ***(Samuels et al., 1998).***

Genotype-phenotype correlation, thoroughly studied over the past few years, suggested that mutations located within the mutational hotspots in codons 680 and 694 are associated with severe disease, early onset, high frequency of attacks, the necessity of a high dose of colchicine to control attacks, and frequent occurrence of amyloidosis in untreated patients ***(Langevitz et al., 2001).***

AIM OF THE WORK

- To study variable clinical presentations of FMF patients.
- Study the incidence of hematological changes detected in Egyptian children with FMF.
- The effect of the disease activity and colchicine therapy on these changes considering the dose and duration of therapy with colchicine.

CHAPTER I

1. Introduction

Familial Mediterranean Fever (FMF) is an inherited disease characterized by sporadic attacks of inflammation affecting the serosal spaces. It occurs primarily among the populations inhabiting or originating in the Mediterranean basin. Despite a striking clinical picture of recurrent bouts of fever and severe abdominal pain, it was not recorded as a distinct clinical entity until 1945 ***(Siegal et al., 1945)***.

Migration of large number of people occurred during the 20th century, FMF cases may now be found all over the world ***(Pras et al., 1998).***

FMF mainly affects populations of the Mediterranean basin, such as Arabs, Armenians, Sephardic Jews and Turks. Carrier frequency has been estimated to reach 1:7 to 1:5 in Armenians and Sephardic Jews, respectively ***(Rogers et al., 1989), (Daniels et al., 1995),*** FMF has also been described in other European populations. ***(Booth et al., 1998; Deckers et al., 1999)***

Definition:

Familial Mediterranean Fever (FMF), is an autosomal recessive condition, affects more than 100,000 people worldwide, and as such, is the most common of the hereditary periodic fevers.

The disease is most prevalent among non-Ashkenazi Jews, Arabs, Turks and Armenians, Yet, it is observed worldwide due to the extensive population movements of the 20th century ***(Kastner et al., 2005).***

The disease typically presents as recurrent episodes of fever accompanied by topical signs of inflammation, mainly involving the peritoneal, pleural and articular cavities. An FMF attack is nearly always accompanied by fever, but it may not be noticed in every case. Some people experience chills prior to the onset of fever. The attacks usually last 48-96 hours, with the peak intensity occurring within the first 12 hours. The time interval between attacks ranges from days to months or even longer***. (Lidar et al., 2006)***

Between attacks, most patients are completely without symptoms. It is not entirely clear what brings on an attack, however people with FMF often report mild physical trauma, physical exertion or emotional stress just prior to the onset of symptoms ***(Daniel et al., 1998).***

Importantly, the severity of the disease is linked to the occurrence of AA (Amyloid A) amyloidosis which is the most serious histopatholigical finding in FMF. Amyloid is deposited in the intima and media of arterioles and in subendothelium of venules in all major organs. There is also parenchymal deposition of amyloid, particulary in the renal glomeruli, adrenals,spleen and alveolar septa of the lung , while the liver and heart are characteristically spared ***(Bakkaloglue et al., 2003).***

Given the absence of pathognomonic clinical or easily available biochemical abnormalities, the diagnosis of FMF was until recently based on clinical suspicion and the use of criteria. The diagnosis of FMF may be extremely difficult to establish in the presence of atypical signs, and

with late onset and absence of family history or at-risk background. However, it is crucial to establish the diagnosis of FMF, since it leads to the beginning of a daily and lifelong administration of colchicine, which is an efficient preventive treatment of both the attacks and amyloidosis ***(Zemer et al., 1986).***

The gene responsible for FMF (MEFV) ***(Mediterranean Fever***) situated on the short arm of chromosome 16 (16p13.3) has been identified by positional cloning ***(The French FMF Consortium, 2002)***, and encodes a protein named marenostrin or pyrin. The spectrum of MEFV mutations responsible for FMF has been regularly widening, and about fifteen mutations have been discovered. These molecular methods now constitute a powerful tool to establish the diagnosis of FMF in patients with clinical criteria. However, the diagnostic value of the molecular tests in patients with atypical or mild signs, especially in those who do not satisfy clinical criteria, is unknown. ***(Bernot et al., 1998).***

Table (1): Tel-Hashmoer criteria for the diagnosis of familial mediternean fever

Major criteria
Recurrent febrile episodes accompanied by pritonitis, synovitis or pleuritis
Amyloidosis of AA-type without predisposing disease
Favourable response to continous colchicine treatment

Minor criteria
Recurrent febrile episodes
Erysipelas-like erythema
FMF in first degree relative
Definitive diagnosis: 2 major or 1 major and 2 minor **Probable diagnosis: 1 major and 1 minor**

Tel-Hashomer criteria for the diagnosis of Familial Mediterranean Fever (FMF***) (Livneh et al., 1997).***

Common Manifestations

Common manifestations of FMF type 1 include the following:

Recurrent fever

Recurrent fever during early childhood may be the only manifestation of FMF, It is present in 96% of inflammatory episodes; body temperature can reach very high values, even over 40°C; it usually appears suddenly and lasts from 12 to 72 hours and is preceded by shivers in about 20-30% patients***. (Shohat et al., 2011)***

Abdominal attacks

These are experienced by 90% of affected individuals and start with the sudden onset of fever and pain affecting the entire abdomen. Physical examination reveals board-like rigidity of the abdominal