Familial Mediterranean Fever: Review of Literature and Report of Two Cases

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Abstract

Familial Mediterranean fever, an autosomal recessive disorder, is a member of the periodic fever syndromes, and considered to be the most common cause of recurrent febrile episodes in children. It is important to understand the disorder as familial Mediterranean fever falls on a spectrum of various presentations; the recurrent episodes of familial Mediterranean fever may be so severe that the quality of life may be affected in such patients. Therefore, physicians should not delay the evaluation in such cases and promptly initiate treatment to not only improve quality of life but to also avoid complications, such as amyloidosis.

This study reports two different cases of familial Mediterranean fever, with varying clinical presentations, and established diagnosis via genetic testing as well as cessation of symptoms with a trial of therapy. Furthermore, this study discusses the various manifestations of familial Mediterranean fever, laboratory findings, and current therapies available for management.

Key Words: Children, Familial Mediterranean fever, Hereditary Periodic Fever Syndromes.

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1- INTRODUCTION

Familial Mediterranean Fever (FMF) is an autosomal recessive, autoinflammatory diseases characterized by sporadic and recurrent episodes of fever and serosal inflammation. The serositis can present as abdominal pain, chest pain, or joint pain, and can also be accompanied with other findings such as an erysipelas-like skin lesions, acute pericarditis, acute scrotum, febrile myalgia syndrome, headaches, and/or aseptic meningitis (1). The clinical features of FMF fall on a spectrum of different variations and severity in symptoms. While FMF is not restricted to specific ethnic groups, it is reported as most prevalent in individuals of Turkish, Armenian, North African, Jewish, and Arab descent; it is also reported at a lower prevalence in other ethnicities such as Greece, Italy, and even Japan (2).

Mutations in the (Mediterranean fever) (MEFV) gene, located on the short arm of chromosome 16, can lead to FMF. MEFV is responsible for the production of the amino acid, pyrin, also known as marenostrin; pyrin is most prominent in the cytoplasm of mature monocytes, neutrophils, eosinophils, dendritic cells and synovial fibroblasts (3). While the full role of pyrin is not very well understood, it is hypothesized to play a role in the regulation of apoptosis, inflammation and cytokines, and primarily suppresses the inflammatory response (4). Pathogenic mutations in the MEFV gene lead to the disrupted activity of the pyrin protein, which interrupts the control of the inflammatory process, leading to an inappropriate or prolonged inflammatory response, even in the absence of any triggers, inducing the characteristic pain episodes (serositis) seen in FMF (1).

Due to the lack of development of one specific diagnostic test to diagnose FMF, the diagnosis primarily remains clinical, depending on the collective findings of clinical symptoms, family history/ethnicity, lab tests, and genetic tests (1). Furthermore, the genetic testing is used to support and aid in the diagnosis of FMF, and should not be used to exclude FMF. In suspected individuals of FMF who meet the clinical criteria, but the genetic test is not diagnostic, then a six-month trial of colchicine therapy with relief of symptoms can support the diagnosis of FMF (5). We are presenting two cases with established diagnosis of familial Mediterranean fever.

2- CASE REPORT

2-1. Case 1: Patient A

A 2-year- old Caucasian male is presented to Pediatric Rheumatology for evaluation of recurrent episodes of fever, abdominal pain, skin rash (red macular rash), headache, eye pain, and swelling in the face and extremities. These episodes have been occurring in the past 2 months at irregular intervals; symptoms resolve with corticosteroid dose. Mother describes these "attacks" to be so severe and discomforting, prompting multiple emergency department (ED) evaluations. Patient has a history of gastro-esophageal reflux since infancy and milk protein intolerance. He has been previously evaluated by Allergy and Immunology, for which antihistamine was prescribed for possible allergies and idiopathic angioedema and urticaria.

Allergy testing was negative as well as testing for hereditary angioedema. Physical exam is unremarkable; no active signs of abdominal pain, arthritis, dermatitis, or lymphadenopathy. His laboratory findings were non-significant; normal complete blood count values, inflammatory markers, and serum immunoglobulin D (IgD). Family history is not significant; no family history of similar symptoms, nor belonging to prevalent populations of familial Mediterranean fever (Mediterranean descent). Tumor Necrosis Factor Receptor

Associated Periodic Syndrome (TRAPS) genetic testing was negative; however, MEFV genetic analysis concluded a single copy of "variant undetermined clinical significance", thereby, non-conclusive of familial Mediterranean fever, but cannot rule out familial Mediterranean fever as a diagnosis. Subsequently, he was evaluated for abdominal pain (endoscopy and colonoscopy), and headache (Head MRI); to which all tests proved negative. Regardless of the non-diagnostic genetic testing for familial Mediterranean fever, it was then planned to initiate a diagnostic and therapeutic trial of colchicine. Upon follow up after three months of colchicine therapy, the patient's symptoms have subsided with the initiation of colchicine therapy, and mother describes improvement in patient's quality of life.

2-2. Case 2: Patient B

A 6 ½ - year- old male, born in Turkey, referred by his primary care physician for possible diagnosis of familial Mediterranean fever. Patient complains of recurrent febrile episodes accompanied with severe abdominal pain for past 1 ½ year; these episodes last for two days for which he takes ibuprofen to relieve his pain, elevated C-reactive protein has also been documented during attacks. Patient reports prior to onset of these episodes, he has viral infections, and sometimes the viral infections and abdominal pain episodes overlap. These attacks are recurrent, and often patient can predict the onset of these attacks. Due to severe recurrent abdominal pain, patient has had an extensive evaluation, including appendectomy, although pathology report of appendix showed no appendicitis. He has also had an endoscopy and colonoscopy in which all results were normal. Family history is as follows: both parents are Turkish, and paternal aunt reports some similar symptoms relating to "stomach pain", however no other similar symptoms attributing to familial

Mediterranean fever reported. Genetic testing showed the patient to be homozygous for M694V mutation in the MEFV gene, which is consistent with diagnosis of familial Mediterranean fever. Patient was then started on daily treatment of colchicine therapy.

3- DISCUSSION

3-1. Epidemiology and Prevalence

FMF is reported to be most prevalent in populations belonging to the Mediterranean descent: Arabs, Armenians, Turkish, Greek, Italians, Persians, North African Jews, and Sephardic and Ashkenazi Jews from Eastern Europe (6, 7). Though not restricted to the previous mentioned ethnic populations, FMF has also been reported at a lower prevalence in non- Mediterranean descent, such as Japanese, Chinese, European, and South American populations (8, 9). Geographically, Turkey ranks the highest with the most number of FMF patients; a review reported a prevalence varying between 1:150 and 1: 10,000. Subsequently, the prevalence in Israel is estimated more than 1: 1,000 depending upon the ethnic group studied (Ashkenazi or non- Ashkenazi Jews) (2). Next, Armenians are the most widespread frequent ethnic group affected with a reported prevalence of 1:500 (1). In recent studies, FMF has now been reported in countries such as Japan, US, Greece, France, Germany, and Italy (9).

3-2. Pathogenesis

The immune system is divided into two divisions: the innate arm and the adaptive arm. Over exaggeration of the adaptive immunity is the pathogenesis of many autoimmune disorders; resulting in increased self-reactive lymphocytes and autoantibodies. On the other hand, autoinflammatory syndromes, also known as the periodic fever syndromes, are an umbrella of disorders characterized by the

hyperactivation of the innate immunity in the absence of any trigger or stimulus, resulting in recurrent episodes of fever and inflammation (10). FMF occurs as a result of point mutations (missense) in the MEFV gene, located on the short arm of chromosome 16, which codes for the protein, pyrin; mainly expressed in the cells of the innate immunity: neutrophils, monocytes, and dendritic cells (10). These mutations lead to the abnormal function of inflammasomes, which are multiprotein structures that serve to activate caspase-1, an enzyme that mediates proteolytic processing and the further activation of proinflammatory cytokines and mediators of inflammation: interleukin (IL)-1B, IL-18, TNF-a, IL-6, IL-17, type 1 interferons (IFN-a and IFN-b), and the complement system (11). The excessive production of IL-1B produces harmful systemic effects (and is the main pathogenesis underlying the autoinflammatory syndromes) such as fever, hypotension, tissue damage, bone resorption, accumulation of neutrophils at involved sites (neutrophilia-neutrophil dominant inflammation), increased concentrations of the acute phase reactants, C-reactive protein (CRP) and serum Amyloid A (SAA), and at extreme higher concentrations can produce hemodynamic shock. The increased level in the acute phase reactants over time leads to amyloidosis which promotes further tissue damage (12, 13).

Structurally, the pyrin protein contains four domains: (a) the pyrin domain (PYD); (b) the B box zinc finger; (c) alpha helix; and (d) B30.2 (PRYSPRY), with the most point (missense) mutations found in this domain. Each of these domains forms specific protein-protein interactions leading to downstream effects with the resultant role in regulation of innate immunity, inflammation and host defense. While it is agreed that pyrin plays a role in the suppression of the inflammatory response, controversy exists whether pyrin

is a positive regulator or negative regulator of caspase-1 activation (3). Ozkurede and Franchi proposed two models, the "Proinflammatory model" and the "Anti-inflammatory model" for the possible explanation of the defective pyrin and its role in FMF (11). The "Proinflammatory model" hypothesizes that under normal circumstances, in response to a specific stimulus (endogenous or exogenous), the pyrin protein via its formation of protein-protein bonds, activates the inflammasome structure and subsequently activates caspase-1; yielding a proper inflammatory response to fight off an infection. The mutation in this model is a dominant gain of function. Therefore, the mutant pyrin protein is capable of constructing the inflammasome in the absence of any trigger or stimulus; resulting in the over activation of caspase-1 and the subsequent excess production of the proinflammatory cytokines, namely IL-1B and IL-18 (11).

In the alternative, pyrin is a negative regulator of caspase-1; here the loss of function mutation results in the failure to control the activation of caspase-1 (no longer inhibits the enzyme), thereby leading to the excess secretion of IL-1B (11). Nevertheless, the endpoint of a defective pyrin function is the overproduction of the proinflammatory cytokines (IL-1B), and other mediators of inflammation, clinically resulting in an attack of FMF (fever and serositis). Overall, the outcome is a state of unopposed inflammation.

3-3. Genetics

The MEFV gene consists of 10 exons in which mutations have been found on the following exons: 1, 2, 3, 5, 9, and 10. Of these exons, 4 of the 5 founder mutations responsible for FMF occur on exon 10: M680I, M694V, M694I, and V726A; 1 founder mutation occurs on exon 2: E148Q. These 5 founder mutations account for over 80% of FMF cases in

population belonging to the Mediterranean descent, with M694V being reported as the most frequent mutation (20-65%) (14). The clinical picture associated with MEFV mutations ranges from incomplete penetrance (absence of symptoms), variable expression, to severe complications (amyloidosis). M694V homozygotes show 99% penetration and are associated with a severe disease form: early disease onset, amyloidosis, arthritis, or increased frequency of attacks (15). On the contrary, the E148Q mutation is reported to be the least penetrant and associated with a mild form of the disease to a silent phenotype (even in homozygotes). Similar studies also report higher carrier frequencies (>10%) amongst healthy individuals versus patients with FMF. For this reason, many researchers are questioning whether this should be considered as a benign polymorphism rather than a mutation (16).

3-4. Clinical Manifestations

FMF is divided into 2 phenotypes: Type 1 is characterized recurrent episodes of fever and serosal inflammation: peritonitis, pleuritis, synovitis, and rarely pericarditis and meningitis. Type 2 is characterized by amyloidosis as the first and only presentation in an otherwise asymptomatic individual (typical attacks of FMF are absent) (2). Disease onset is usually under 20 years of age (90% of cases) or under 10 years of age (60% of cases); typically develops as sudden, unprovoked, recurrent episodes of fever and serositis (manifested as either abdominal pain, chest pain, arthritis, etc.) lasting 1-4 days and resolves spontaneously. The frequency of these attacks may vary but can be seen up to once a week or a few years; the interval between these episodes generally is asymptomatic, however arthritis and myalgia may have a prolonged course (4). Usually FMF patients are unable to identify a specific trigger; however, reported inciting events may include: viral

illness, stress (emotional, mental, and physical), high-fat diet, extremes of temperature, and menstruation in women (5). Some patients may even experience a prodromal phase 17-24 hours prior to the onset of an episode. These symptoms may be described as a period of discomfort, anxiety, irritability, and even psychological disturbances (1).

3-4-1. The following are common clinical manifestations of Type 1 FMF

• **Fever**

While fever can coincide with serositis, a high fever may be the only presenting symptom without any additional features during the episode. This is especially true in younger children, making this feature an essential component to the diagnosis. The temperature is generally above 38C; usually lasting 2-4 days (but can last longer), and resolves spontaneously (4).

• **Abdominal Pain**

Abdominal pain results from the peritonitis and is the most frequent complaint observed in 90% of FMF patients. Initially the pain is localized, and then spreads to become more generalized. Signs of peritonitis are present on physical examination: guarding, rigidity, rebound tenderness, and loss of peristaltic sounds. These findings can lead to a misdiagnosis of "acute abdomen" leading to a delay in diagnosis and sometimes unnecessary surgeries; however, the episode generally resolves in 24-48 hours (13).

• **Arthralgia/ Arthritis**

Observed in approximately 75% of FMF patients; characterized by sudden attacks of joint pain, usually monoarticular, that can be brought on by minor trauma, such as prolonged walking. Joints may resemble septic arthritis clinically: red, swollen, erythematous, and tender; symptoms generally resolve after peaking 24-48

hours but can take up to a week to resolve, with no joint damage or deformity. The most common joints involved are large joints such as knee, hip, or ankle; other joints can be involved too (i.e. shoulder, wrist). Some studies reported recurrent monoarthritis as the sole feature in FMF. While short acute attacks of monoarthritis is typically common in FMF, in a subset of patients chronic monoarthritis can also occur. In these cases, attacks subside after weeks or months, resulting in severe joint damage and deformities (1, 13).

- **Chest Pain**

Observed in 45% of FMF patients; sudden onset of unilateral chest pain which aggravates with breathing or coughing; diminished breath sounds on affected side. Resolves within 1-3 days, but can last up to a week (4).

- **Erysipelas-like skin lesion**

The erysipelas- like skin lesions can mimic infectious erysipelas or cellulitis and are often misdiagnosed as such. These lesions usually last 1-2 days and described as erythematous, tender, raised lesions, measuring 10-35 cm^2 in size mainly on lower legs or dorsum of foot. Recovery is spontaneous and antibiotics are not advised (17).

3-4-2. The following are rare clinical manifestations of FMF:

- **Pericarditis**

Pericarditis is reported in less than 1% of patients with FMF; compared to the serosal involvements of other parts of the body, the pericardial membrane is reported as a rare occurrence. The attacks last an average of 4-7 days, but can take up to 14 days to resolve. Symptoms include: chest pain, which is sharp and pleuritic (improved with sitting up and leaning forward), friction rub; ST segment elevations seen on Electrocardiogram (ECG, EKG) (18).

- **Protracted Febrile Myalgia (PFM)**

The incidence of PFM is reported to be 1-3% in patients with FMF; however, it is considered a severe debilitating myalgia which affects the patient's quality of life. Symptoms include: high grade fever, intense pain and sensitivity particularly in lower limbs. PFM can also be associated with abdominal pain, diarrhea, arthritis, and a purpuric rash which can resemble Henoch- Schönlein purpura (HSP). Unlike the short acute attacks of FMF, the episode of PFM can last for 4-6 weeks; some studies suggest that for the pain to be labeled as PFM, it should last at least 5 days (19). Despite the intensity of pain, there are no significant findings on laboratory work (muscle enzymes normal), muscle biopsy, and EMG. PFM is reportedly more frequent in M694V homozygous individuals with FMF; while no inciting event has been established for PFM, some studies report finding high Antistreptolysin O (ASO) titers, which could suggest recent streptococcal infection as a trigger. While most typical episodes of FMF resolve spontaneously, public financial management (PFM) responds to corticosteroids (20).

- **Exertional Myalgia**

Post-exercise myalgia usually affects lower limbs; usually lasts 2-3 days and begins in the evening. This episode does not respond to treatment with colchicine, rather it resolves with rest or treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (1).

- **Renal findings other than amyloidosis**

While amyloidosis without a doubt remains a significant complication of FMF and determines the overall prognosis, approximately 22% of patients with FMF

reported renal problems other than amyloidosis. Renal findings include: hematuria, proteinuria, acutePyelonephritis, tubulointerstitial nephritis, and glomerulonephritis (1).

- **Other rare atypical features**

Acute Scrotum

➢ Characterized by unilateral, redness, pain and swelling of scrotum (4),

Vasculitides

➢ Some studies report a higher incidence of the following vasculitides among FMF patients: such as HSP, polyarteritis nodosa, and Behcet's syndrome (4), and

Headache and Aseptic meningitis (1).

- **Clinical Diagnosis**

The diagnosis of FMF is made clinically; features suggestive of FMF include recurrent febrile episodes associated with serositis (abdominal pain, chest pain, arthritis), lasting approximately 1-4 days and resolves spontaneously. The clinical picture is further supported by evidence of family history, ethnicity, laboratory findings, genetic testing, and response to colchicine treatment (13). The Tel Hashomer criteria (based on major and minor criteria), developed at the Tel

Hashomer Medical Center, has been the most commonly used approach worldwide in diagnosing FMF. While the Tel Hashomer criteria has been successful in diagnosing adult patients with FMF, the specificity is low in children (55%) (1). Per Livneh et al., the diagnostic criteria proposed in the Tel Hashomer set are poorly defined; some clinical features of the attacks may differ in children than adults, and children might poorly describe the severity and location of their pain (21).

The diagnostic criteria suggested by Livneh et al. expands on the Tel Hashomer criteria by accurately defining features and further classifying into typical, incomplete, and supportive. Furthermore, certain changes were made in the previous set of criteria; such as removing amyloidosis as a major criterion for diagnosing FMF. Currently, due to prompt recognition and early management of FMF, amyloidosis rarely occurs as the sole manifestation (Type 2 FMF) and therefore is no longer included. Rather, including incomplete abdominal attacks as part of the major criteria in diagnosing FMF proves to be sufficiently strong evidence for FMF and increased the sensitivity and specificity of the criteria set. As the criteria set proposed by Livneh et al. was detailed, a simple version has been adapted and can be used interchangeably (22, 23) (**Tables.1, 2**).

Table-1: Tel Hashomer Criteria

Major	Minor
Recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis)	Recurrent febrile episodes
Amyloidosis of AA type without a predisposing disease	Erysipelas- like erythema
Favorable response to regular colchicine treatment	FMF in a first-degree relative

Definitive diagnosis based on Tel Hashomer criteria: 2 major, or 1 major + 2 minor; Probable diagnosis: 1 major + 1 minor.

Table-2: Simplified criteria set for diagnosis of FMF according to Livneh et al.

Major	Minor
Typical attacks: • Peritonitis (generalized) • Pleuritis (unilateral) or pericarditis • Monoarthritis (hip, knee, ankle) • Fever alone.	Incomplete attacks involving 1 or more of the following sites: • Chest • Joint
Incomplete abdominal attack	Exertional leg pain
	Favorable response to colchicine

Diagnosis according to simplified criteria: at least 1 major or at least 2 minor criteria.

- **Major criteria:**
  - Typical attacks
    - Peritonitis (generalized)
    - Pleuritis (unilateral) or pericarditis
    - Monoarthritis (hip, knee, ankle)
    - Fever alone
- **Minor Criteria:**
  - Incomplete attacks involving 1 or more of the following sites:
    - Abdomen
    - Chest
    - Joint
  - Exertional leg pain
  - Favorable response to colchicine
- **Supportive Criteria:**
  - Family History of FMF
  - Appropriate ethnic origin
  - Age <20 years at disease onset
  - Features of attacks:
    - Severe requiring bed rest
    - Spontaneous remission
    - Symptom-free interval
    - Transient inflammatory response, with 1 or more abnormal test result(s) for white blood cell count, ESR, SAA, and/or fibrinogen
  - Episodic proteinuria/ hematuria
  - Unproductive laparotomy or removal of white appendix
  - Consanguinity of parents

Diagnosis of FMF according to Livneh et al.:

- At least 1 major criteria
- At least 2 minor criteria

Fig.1: Detailed diagnosis Criteria set suggested by Livneh et al.

Typical attacks are defined by the presence of all the following features:

- Pain due to serositis,
- Recurrence of attacks (at least 3 of the same type),
- Presence of fever (rectal temperature $\geq$ 38 °C or higher),
- Short duration (12 hours to 3 days).

Incomplete attacks (painful and recurrent) are defined as not fulfilling the criteria for a typical attack. For instance: temperature <38 °C; duration of attack either less than what is specified but no less than 6 hours and no more than 7 days; no signs of peritonitis during the abdominal attack; localized abdominal attacks (versus generalized); arthritis in other joints than what is specified (21, 22).

3-5. Laboratory Findings and Genetic Testing

As FMF is a member of the autoinflammatory syndromes, laboratory studies during the acute episodes reveal elevated markers of systemic inflammation. Common findings include leukocytosis (neutrophil-predominant inflammation), elevated acute phase reactants which include C-reactive protein (CRP), erythrocyte- sedimentation rate (ESR), fibrinogen, and serum amyloid protein (SAA). Urinalysis performed during episodes may be normal or show transient hematuria or proteinuria; proteinuria should raise concern for amyloidosis (1).

Genetic testing is carried out by two methods: targeted mutation analysis or full gene sequencing. The targeted mutation analysis allows for the testing of the most frequent gene mutations identified and is generally the first approach. Although five prevalent mutations have been identified in high risk individuals with FMF, laboratories generally test for a total of twelve common MEFV mutations, as individuals can be homozygotes or compound heterozygotes for these mutations. If the targeted mutation analysis is non-diagnostic (detects either no mutation, or one mutation versus two), full MEFV gene sequence analysis can be employed (6, 10). While the understanding of FMF is autosomal recessive, detecting two pathogenic mutations in the MEFV gene confirms the diagnosis. However, there have been reports of finding either one pathogenic mutation, or no mutations at all in a clinically apparent FMF patient. This raises the question of either possible dominant inheritance, whether a second mutation has been missed due to its location out the analyzed gene region, or the finding of a new rare mutation (24).

Booty et al. conducted a study in 46 patients clinically diagnosed with FMF carrying one MEFV mutation in search for a second mutation in the MEFV gene. Both methods of genetic tests were used (targeted gene analysis and full gene sequence analysis), but failed to identify a second mutation. The study concluded that the finding of a single MEFV mutation in the presence of highly suggestive clinical symptoms for FMF, was sufficient for the diagnosis and commencement with a trial of colchicine therapy. Therefore, in individuals in which the clinical picture is in favor of diagnosis and molecular testing is not diagnostic, relief of symptoms with initiation of a six-month trial of colchicine therapy, and subsequent recurrence of attacks with cessation of treatment can serve as confirmation of diagnosis (25).

3-6. Differential diagnosis

Fever in a child is a very common presenting complaint to the primary care physician (PCP); it is the job of the PCP to evaluate the child and propose a satisfying differential diagnosis. Before concluding to the autoinflammatory syndromes, it is important to rule out other differentials of febrile episodes in children, such as

infection (viral, bacterial), or other diseases such as inflammatory bowel disease (IBD), rheumatic fever, or systemic juvenile idiopathic arthritis (26). Nevertheless, when other diagnoses have been excluded, periodic fever syndromes should be considered especially if there are strong characteristic clues in the patient's history and/or family history. The periodic fever syndromes are an umbrella of disorders in which each disease has overlapping features and distinguishing characteristics, but overall are characterized by febrile episodes and systemic inflammation.

The major periodic fever syndromes include: Familial Mediterranean Fever (FMF); Tumor necrosis factor (TNF) receptor-1 associated periodic syndrome (TRAPS); Hyperimmunoglobulin D Syndrome (HIDS); Cryopyrin-associated periodic syndromes (CAPS); periodic fevers with Aphthous Stomatitis, pharyngitis, and adenitis (PFAPA); pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA); Blau syndrome; syndromes associated with deficiency of IL- alpha receptor antagonists; and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) (27).

3-7. Disorders of the periodic fever syndromes with brief descriptions

3-7-1. Periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA)

The most common cause of periodic fevers in children; characterized by recurrent febrile episodes, lasts 3-6 days, and almost always occurs at regular intervals (approximately 3-6 weeks). The striking feature in this syndrome is the "clockwork" regularity of febrile episodes; according to studies, the intervals are so regular that many families can actually predict the onset of fever (27). However,

the associated symptoms in PFAPA can vary; while some members of the periodic fever syndromes show monogenic heredity (either autosomal dominant or recessive pattern) as the etiology, most disorders still have no known clear genetic cause or inheritance pattern, such as Periodic Fevers with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) (26). Rather most children presenting with periodic fevers are not found to have any genetic mutations in the genes known to cause periodic fever syndromes. Regardless of the etiology, because these disorders share similar autoinflammatory features, they are included in the differential of periodic fevers in children. The typical presentation of PFAPA is usually in children, with febrile episodes occurring at regular intervals, pharyngitis, cervical adenitis, and aphthous stomatitis are common symptoms.

Other symptoms may include abdominal pain, myalgias, arthralgia, headache, nausea, vomiting, or fatigue. Lab findings show leukocytosis and increased acute phase markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], Serum amyloid A [SAA], fibrinogen, ferritin); because there is no confirmatory testing for PFAPA, the diagnosis remains clinical. PFAPA is treated with either prednisone (at the onset of fever), or tonsillectomy (28).

3-7-2. TNF receptor associated periodic fever syndrome (TRAPS)

Autosomal dominant, characterized by prolonged recurrent febrile episodes accompanied with attacks of systemic inflammation. TRAPS is caused by mutations in the TNF-1a receptor, resulting in the overproduction of inflammatory cytokines and subsequent systemic inflammation. The attacks may occur approximately every 5-6 weeks, lasting 3-6 weeks, and associated with prolonged episodes of fever, rash,

myalgias, peritonitis, pleuritis, arthralgias, or conjunctivitis. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids may be effective in the acute attacks, however etanercept has been shown to reduce the frequency and severity of episodes (26).

3-7-3. Hyperimmunoglobulin D syndrome (HIDS)

Autosomal recessive; characterized by recurrent episodes of fever, systemic inflammation, and cervical lymphadenopathy lasting 3-7 days. Symptoms include repeated attacks of fever, chills, cervical lymphadenopathy, abdominal pain, hepatosplenomegaly, rash, arthralgia/arthritis, or headaches. HIDS can be differentiated on the basis of earlier age of onset, lengthened periods of episodes, along with lengthened intervals between episodes. Although lab values are similar to that of other periodic fever syndromes, the majority of patients in HIDS have elevated IgD (>100 IU/dL) and increased urinary levels of Mevalonic acid (MVA) which is helpful in making the diagnosis. Additionally, testing for the mevalonate kinase (MVK) gene mutations is used to diagnose HIDS. Treatment is with a trial of NSAIDs, corticosteroids, anakinra, or etanercept (26-28).

3-7-4. Cryopyrin- associated periodic syndromes (CAPS)

A rare autosomal dominant syndrome, that can be distinguished from other members of the periodic fever syndromes by the presence of an urticaria-like skin rash, fever, and the presence of cold exposure as a trigger for the episodes. CAPS is associated with mutations in NLRP3, which codes for cryopyrin; NLRP3 is a component of the inflammasome located in neutrophils, monocytes, and chondrocytes. The mutation results in over activation of the inflammasome, with the resultant release in inflammatory cytokines (mainly IL-1B) in the absence of any stimulus and leads to a pro-inflammatory state. The discovery of NLRP3 led to the linking of three syndromes ranging in severity: familial cold autoinflammatory syndrome (FCAS), Muckle- Wells syndrome (MWS), and chronic infantile neurological cutaneous articular syndrome (CINCA)/ neonatal- onset multisystem, inflammatory disease (NOMID) (26-28).

3-7-5. Familial cold autoinflammatory syndrome (FCAS)

Considered as the mild form; symptoms include brief episodes (which lasts less than 24 hours) of fever, urticaria-like skin rash, and arthralgias that are triggered by exposure to cold temperatures (27).

3-7-6. Muckle- Wells Syndrome (MWS)

Mild form of CAPS; in addition to fever, urticaria-like rash, and arthralgias, patients with MWS progressively develop hearing loss due to cochlear inflammation. This form of CAPS is not associated with cold exposure (27).

3-7-7. Chronic infantile neurological cutaneous articular syndrome (CINCA)/ Neonatal onset multisystem inflammatory disease (NOMID)

The most severe form of CAPS in which symptoms are seen in the newborn period. Characterized by persistent episodes of fever, rash, chronic meningitis, blindness, hearing loss, and cartilaginous/ bone deformities (27).

3-7-8. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA)

An autosomal dominant condition characterized by the presence of recurrent painful flares of arthritis and skin manifestations varying from ulcerations, pyoderma gangrenosum, cystic acne, or pathergy. PAPA is treated with anakinra and infliximab (27).

3-7-9. Blau Syndrome

An autosomal dominant condition distinguished by granulomatous inflammation in the skin, eye, and joints. Skin involvement is manifested as a maculopapular rash with dermal granulomas; granulomatous inflammation in the eye leads to uveitis and consequently developing glaucoma and blindness; arthritis usually affects the hands and feet and leads to synovitis and tenosynovitis. Biopsy reveals non-caseating granulomatous inflammation; while management of Blau syndrome has not been standardized, treatment options include methotrexate, thalidomide, corticosteroids, and TNF inhibitors (27).

3-7-10. Deficiency of IL-1a receptor antagonist (DIRA)

An autosomal recessive disorder caused by a mutation in the IL1RN gene, which codes for the interleukin-1 receptor antagonist. Under normal circumstances, the IL-1 receptor antagonist functions to inhibit the pro-inflammatory cytokines (IL-1a and IL-1B); the mutation in the IL1RN gene results in the over stimulation of the pro-inflammatory cytokines. DIRA, also known as osteomyelitis, sterile multifocal, with periostitis and pustulosis (OMPP), usually presents soon after birth with fetal distress, pustular skin rash, arthritis, periostitis, sterile osteomyelitis, and pain with movement in the absence of fever. If left untreated, death can occur from multiorgan failure; treatment with anakinra results in remission of the disease (27).

3-7-11. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)

The onset of this disorder usually begins shortly after birth, and is continuously present from six months of age. Presented with daily fever, purpuric skin lesions, persistent periorbital edema, arthralgias, progressive lipodystrophy, lymphadenopathy, and microcytic anemia. Treatment includes methotrexate, calcineurin inhibitors, TNF inhibitors, and anti-IL1 and anti-IL6 therapy (27).

3-8. Complications

3-8-1. Secondary Amyloidosis

In chronic inflammatory conditions, where there is prolonged ongoing inflammation as a result of pro-inflammatory cytokines, this leads to increased hepatocyte production of an acute phase reactant, serum amyloid A (SAA). Subsequently, SAA is broken down into smaller fragments by monocytes and macrophages, which deposit into tissues, such as kidneys, heart, gastrointestinal tract, spleen, etc. Consequently, over time these deposits damage tissue, leading to the progressive development of secondary amyloidosis (AA) (1). Amyloidosis is the most common complication in untreated FMF; widespread amyloid deposition occurs in tissues, but primarily affects the kidneys (renal amyloidosis). Renal amyloidosis progresses from asymptomatic proteinuria, to symptomatic nephrotic syndrome, and eventually end stage renal disease; this progression can take up to anywhere from 2-13 years to develop after the onset of proteinuria (6).

However, due to established modalities to rapidly diagnose FMF, and initiation of treatment with colchicine without any delays has led to a decrease in the incidence of amyloidosis in prevalent populations; prior the incidence has been reported as high as 60-75%. Nevertheless, amyloidosis still determines the prognosis of FMF and its progression to end stage renal disease; it is important for patients to be evaluated for proteinuria (1). Several studies have reported a higher incidence of amyloidosis in Sephardic Jews versus Ashkenazi Jews; furthermore, the incidence of amyloidosis differs between populations belonging to the same

ethnicity but living in different geographical locations (6). Schwabe et al. reports an incidence of amyloidosis in Armenians living in Armenia is 24%, while the incidence of amyloidosis in Armenians living in California is 0% (29). Additionally, numerous studies have reported a higher risk of amyloidosis and a more severe disease course in patients with FMF who are homozygous for the M694V mutation in the MEFV gene (1).

3-8-2. Small bowel obstruction (SBO)

Recurrent attacks of peritonitis lead to the development of adhesions, and chronically results in small bowel obstruction (1).

3-8-3. Infertility

Infertility observed in females is due to the mechanical obstruction in fallopian tubes from adhesions; in men, amyloid deposition in testes (testicular amyloidosis) results in azoospermia or oligospermia (1).

3-8-4. Treatment

The goal of therapy in patients with FMF is to prevent acute attacks; treat acute episodes; minimize inflammation between episodes; and to prevent the progression of amyloidosis. Colchicine is the gold standard therapy and should be initiated once the diagnosis of FMF is confirmed and continued lifelong (1). The anti-inflammatory effect of colchicine is via microtubule disruption in neutrophils, thereby preventing neutrophilic migration in the inflammatory process. Additionally, colchicine also alters the distribution of cell adhesion molecules on neutrophils and endothelial cells; resulting in a decreasing neutrophil migration, a key step in the neutrophil extravasation in the inflammatory process (13). Side effects of colchicine include: abdominal pain, nausea, vomiting, diarrhea, hematological toxicity (leukopenia, bleeding, easy bruising), and myotoxicity (especially in patients with renal impairment). While

colchicine is the mainstay drug of choice for FMF, it is important for patients to take them continuously as it prevents the attacks and amyloid deposition. Patients should be educated regarding compliance with medication; noncompliance or interruption of colchicine treatment will be followed by febrile attacks and can occur more frequently (30). Furthermore, the risk of progression to end stage renal disease is higher. Taking colchicine at the onset of an attack, or increasing its dose during the acute attack is of no value and does not halt the attack/ symptoms; supportive measures, such as bed rest, NSAIDs, or steroids may be administered for temporary relief of symptoms during the attack (1, 30).

After initiation of colchicine, it is important to follow patients to assess the therapeutic effect and adjust dose as needed. Once the dose of colchicine has been established, patients should further be evaluated every six months for toxicity and response to therapy. Drug toxicity is monitored via complete blood count (CBC) for assessing leukopenia; response to colchicine therapy is monitored by ESR, CRP, SAA, and urinalysis for proteinuria (22). However, patients compliant with colchicine treatment and found to have proteinuria should be evaluated for causes other than amyloidosis (4).

Several studies have reported an estimate of 30-40% of patients diagnosed with FMF partially respond to colchicine, 5-10% are colchicine resistant, and an additional 5-10% are colchicine intolerant particularly due to the gastrointestinal side effects (31). Nonetheless, colchicine should not be discontinued due to its protective effect against amyloidosis; studies have reported that compliance with colchicine has resulted in a decreased incidence of clinical renal disease and progression to end stage renal disease (1). Patients who continue to experience symptoms despite colchicine treatment should be re-assessed

for the following: explore other disorders belonging to the periodic fever syndromes other than FMF for diagnosis; noncompliance to therapy; or patients that fall in the 5-10% category of truly being colchicine resistant (32). Patients who experience frequent attacks, or found to have elevated acute phase reactants between attacks (ESR, CRP, SAA) irrespective of taking the maximal dose of colchicine are considered "colchicine resistant". The preferred second line therapy is interleukin-1 (IL-1) inhibition; these include Anakinra, IL-1 receptor antagonist; Rilonacept, IL-1 fusion decoy receptor; and Canakinumab, anti-IL-1B monoclonal antibody (32). Studies have reported that more than two-thirds of colchicine resistant or intolerant patients responded to treatment with anakinra and canakinumab.

Other treatment therapies include biological agents such as, TNF-a inhibitors (thalidomide and etanercept), or anti-IL-6 agent (tocilizumab). Seyahi et al. reports the use of thalidomide and etanercept in being effective in controlling the febrile attacks in colchicine resistant or intolerant patients (33). Nevertheless, limited data exists amongst the use of biological agents and their efficacy and long-term effects, and therefore need to be further investigated. A crucial point to note is that currently, because no studies have proven any beneficial effect of these therapies other than colchicine on amyloidosis, treatment should be maintained with the concomitant use of colchicine at a tolerable dose to prevent amyloidosis.

4- CONCLUSION

The diagnosis of familial Mediterranean fever may prove to be challenging as recurrent febrile episodes in a child may be an overlapping feature of many diagnoses and the lack of specific diagnostic testing. It is indispensable for primary care physicians to promptly recognize periodic fever syndromes, and without a delay in diagnosis initiate treatment to improve quality of life, avoid unnecessary procedures, and long-term complications. Moreover, recurrent febrile episodes accompanied with serositis should raise the suspicion of familial Mediterranean fever; physicians should hold low threshold in such scenarios and promptly evaluate and initiate appropriate treatment.

5- CONFLICT OF INTEREST

The authors had not any financial or personal relationships with other people or organizations during the study. So, there was no conflict of interests in this article.

6- REFERENCES

1. Sari I, Birlik M, Kasifoglu T. Familial Mediterranean Fever: an updated review. European Journal of Rheumatology. 2014; 1: 21-33.

2. Ben-Chetrit E, Touitou I. Familial Mediterranean fever in the world. Arthritis Rheum 2009; 16:1447–53.

3. Stehlik C, Reed JC. The PYRIN connection: novel players in innate immunity and inflammation. J Exp Med 2004; 200:551.

4. Shohat M, Halpern GJ. Familial Mediterranean Fever- a review. Genet Med. 2011; 13: 487-98.

5. Goldstein RC, Schwabe AD. Prophylactic colchicine therapy in familial Mediterranean fever. A controlled, double-blind study. Ann Intern Med 1974; 81: 792.

6. Zadeh N, Getzug T, Grody WW. Diagnosis and management of familial Mediterranean fever: integrating medical genetics in a dedicated interdisciplinary clinic. Genet Med. 2011; 13: 263–69.

7. El-Shanti H, Majeed HA, El-Khateeb M. Familial Mediterranean fever in Arabs. Lancet 2006; 367: 1016–24.

8. Ong FS, Vakil H, Xue Y, Kuo JZ, Shah KH, Lee RB, et al. The M694V mutation in Armenian-Americans; a 10-year

retrospective study of MEFV mutation testing for familial Mediterranean fever at UCLA. Clin Genet. 2013; 84: 55-9.

9. Tomiyama N, Higashiuesato Y, Oda T, et al. MEFV mutation analysis of familial Mediterranean fever in Japan. Clin Exp Rheumatol 2008; 26: 13–17.

10. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet 2001; 9: 473–83.

11. Ozkurede VU, Franchi L. Immunology in clinic review series; focus on autoinflammatory diseases: role of inflammasomes in autoinflammatory syndromes. Clin Exp Immunol 2012; 167: 382-90.

12. Gross O, Thomas CJ, Guarda G, Schopp T. The inflammasome: an integrated view. Immunological Reviews 2011; 243: 136–51.

13. Portincasa P, Scaccianoce G, Palasciano G. Familial mediterranean fever: a fascinating model of inherited autoinflammatory disorder. Eur J Clin Invest. 2013; 43: 1314–27. doi: 10.1111/eci.12170.

14. Solak M, Yildiz H, Koken R, Erdogan M, Eser B, Sen T, et al. Analysis of familial Mediterranean fever gene mutations in 202 patients with familial Mediterranean fever. Genet Test 2008; 12: 341–44.

15. Gershoni-Baruch R, Brik R, Shinawi M, Livneh A. The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever. Eur J Hum Genet 2002; 10: 145–49.

16. Ben-Chetrit E, Lerer I, Malamud E, Domingo C, Abeliovich D. The E148Q mutation in the MEFV gene: is it a disease-causing mutation or a sequence variant? Hum Mutat 2000; 15: 385–386.

17. Lidar M, Doron A, Barzilai A, et al. Erysipelas-like erythema as the presenting feature of familial Mediterranean fever. J Eur Acad Dermatol Venereol 2013; 27:912.

18. Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A. Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF). QJM 1997; 90: 643-7.

19. Kaplan E, Mukamel M, Barash J, Brik R, Padeh S, Berkun Y, et al. Protracted febrile myalgia in children and young adults with familial Mediterranean fever: analysis of 15 patients and suggested criteria for working diagnosis. Clin Exp Rheumatol 2007; 25: S114-7.

20. Sidi G, Shinar Y, Livneh A, Langevitz P, Pras M, Pras E. Protracted febrile myalgia of familial Mediterranean fever. Mutation analysis and clinical correlations. Scand J Rheumatol 2000; 29: 174-6.

21. Livneh A, Langevit P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 10: 1879–85.

22. Bashardoust B. Familial Mediterranean fever; diagnosis, treatment, and complications. J Nephropharmacol 2015; 4(1): 5-8.

23. Yalcinkaya F, Ozen S, Ozcakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009; 48(4):395–8.

24. Özen S. Changing concepts in familial mediterranean fever: Is it possible to have an autosomal-recessive disease with only one mutation? Arthritis and Rheumatism 2009; 60: 1575–77. doi:10.1002/art.24565

25. Booty MG, Chae JJ, Masters SL, Remmers EF, Barham B, Le JM, et al. Familial Mediterranean Fever with a Single MEFV mutation. Where is the second hit? Arthritis Rheum 2009; 60: 1851–61.

26. De Jesus AA, Goldbach-Mansky R. Monogenic Autoinflammatory Diseases: Concept and Clinical Manifestations. Clinical immunology 2013; 147(3):155-74. doi: 10.1016/ j. clim.2013.03.016.

27. Hausmann JS, Dedeoglu F. Autoinflammatory diseases in pediatrics. Dermatol Clin. 2013; 31: 481–94.

28. Cush JJ. Autoinflammatory Syndromes. Dermatol Clin. 2013; 31: 471–80.

29. Schwabe AD, Peters RS. Familial Mediterranean Fever in Armenians: Analaysis of 100 cases. Medicine (Baltimore) 1974; 53: 453-62.

30. Goldfinger SE. Colchicine for familial Mediterranean fever. N Engl J Med 1972; 287(25):1302.

31. Ozen S, Kone-Paut I, Gül A. Colchicine resistance and intolerance in familial Mediterranean fever: Definition, causes, and alternative treatments. Semin Arthritis Rheum 2017; 16: 30330-4.

32. Gül A. Approach to patients with inadequate response to colchicine in familial Mediterranean fever. Best Pract Res Clin Rheumatol 2016; 30: 296-303.

33. Seyahi E, Ozdogan H, Celik S, Ugurlu S, Yazici H. Treatment options in colchicine resistant familial Mediterranean fever patients: Thalidomide and etanercept as adjunctive agents. Clin Exp Rheumatol 2006; 24: S99-S103.