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FAMILIAL MEDITERRANEAN FEVER: A GENERAL REVIEW

Abstract

Familial Mediterranean Fever (FMF) is an autosomal recessive inherited disease, which is accompanied by recurrent attacks of fever and serositis. It can be distinguished into two types. Type 1, is associated with recurrent short episodes of inflammation and polyserositis; type 2, is characterized by the accumulation of serum amyloid A mainly in the kidney leading to amyloidosis. The etiology of this disease is due to mutations in the MEFV gene, which encodes the protein "pyrin". These mutations cause the uncontrolled production of proinflammatory cytokines including interleukin 1. Genetic analysis is important to confirm the diagnosis in the patients. Colchicine is the drug of choice. However, some people are resistant to this drug. In such cases, newer biologic agents have used in the treatment of the disease. This review aims to discuss the most recent advances about FMF including the major symptoms, the diagnosis, the genetics and the management.

Keywords

Familial Mediterranean Fever, amyloidosis, MEFV gene, pyrin, colchicine

1. INTRODUCTION

Familial Mediterranean Fever (FMF) is an autosomal recessive disease with a periodic autoinflammatory pattern that can be distinguished from PFAPA by a family history and a differential diagnosis (Jamilloux et al., 2017). This disorder is mainly affecting the populations from Mediterranean ancestry including Arabs, Turks, Armenians and Jews (Heller et al., 1958). Despite this common prevalence, it can also be found in populations of non-Mediterranean ancestry as some cases were reported in Japanese, Chinese and Korean people (Ben-Chetrit and Levy, 1998; Ben-Chetrit and Touitou, 2009; Lee et al., 2016; Kimura et al., 2018). Although most commonly known as FMF, this disease appeared under various other names, the most used of which were: recurrent polyserositis, periodic peritonitis and periodic disease (Zadeh et al., 2011).

It possesses two phenotypes leading to two types 1 and 2. FMF type 1 includes a variety of mild signs like inflammation, peritonitis, fever and pleuritis. FMF type 2 is more serious since it causes amyloidosis in an asymptomatic individual that affects mainly the kidney (Pras, 1998; Kone Paut et al., 2000; Dember, 2006; Ben-Chetrit and Backenroth, 2001). The main cause of this disease is a mutation in chromosome 16 attacking the MEFV gene (Ostring and Singh-Grewal, 2016). Proinflammatory cytokines related to these mutations including IL-1 β and IL-18 are known to cause excess inflammation (Chae et al., 2006; Kim et al., 2015; Chae et al., 2011). Diagnosis depends on symptoms and it is based on molecular genetic testing and on multiple serum cytokine profiling (Zadeh et al., 2011; Koga et al., 2016). The mainstay of treatment is life-long colchicine drug given daily to reduce the symptoms of the disease (Goldfinger, 1972; Sönmez et al., 2016; Ozdogan and Ugurlu, 2019). Unfortunately, the use of this drug has been complicated by resistance in a minority of patients. Since carriers of FMF show significantly elevated levels of serum TNF alpha, IL-1, and IL-6, FMF patients with insufficient response to colchicine were successfully treated with anti IL-1, anti IL-6, or TNF inhibitors drugs. Therefore, it is best to use colchicine in combination with biologics such as anakinra and canakinumab (Belkhir et al., 2007; Grattagliano et al., 2014; Alghamdi, 2017; Ozdogan and Ugurlu, 2019; El Hasbani et al., 2019). Scientist’s discoveries concerning FMF throughout the years summarized in Table 1.

2. SYMPTOMS OF FMF

2.1. Common Symptoms

Recurrent attacks of fever mainly during the early childhood (El Shanti et al., 2006). The duration of attacks is 1 to 3 days and the time between them is variable depending on the patients (Ostring and Singh-Grewal, 2016).

a. Abdominal attacks

About 95% of the patients experience abdominal pain. Physicians often report signs of rigidity of the abdominal muscles, abdominal distensions and rebound tenderness in patients suffering from FMF (Shohat and Halpern, 2010).

Table 1: This table shows scientist’s discoveries concerning FMF throughout the years.

Dates:	Historical Events:	Ref
Second Century AD	Galen described cyclic fever that he linked to different moon phases	(Reimann, 1951)
Past 200 yrs.	Many authors described a syndrome associated with recurrent attacks of fever ,abdominal ,chest and joint pain	(Adwan, 2015)
1820	Colchicine was named by the French chemists Pellelier and Caventon	(Goldfinger, 1972)
1908	Janeway and Mosenthal described a young girl with intermittent fever and abdominal pain that refer it to FMF instead of any other auto inflammatory syndrome	(Janeway and Mosenthal,1908)
1945	Siegal announced the first exact description of FMF which later appeared under various other names including: Catten-Namou syndrome and periodic disease	(Siegal, 1945)
1948	Reimann who described the term periodic disease explained that many adjectives are used interchangeably before the noun indicating the outstanding characteristic	(Reimann, 1948)
1951	Two French physicians Cattan and Namou realized the association of FMF with renal disease	(Cattan and Namou,1951)

Continue Table 1

1958	-Tuqan at the American University of Beirut in Lebanon indicate the occurrence of amyloidosis -Heller et al confirm the genetic nature of the disease	(Tuqan, 1958; Heller et al., 1958)
1972	Colchicine introduced as a prophylactic treatment in FMF which decreases the hazards of amyloidosis	(Hartung, 1954)
1974	The efficacy of colchicine confirmed through random controlled trails	(Goldstein and Schwabe, 1974; Zemer et al., 1974)
1976	Trails confirmed that colchicine acts by inhibiting leukocyte migration	(Dinarello et al., 1976)
1997	Two distinct groups , American and French, identified the MEFV gene by positional cloning	(The International FMF Consortium; French FMF Consortium)
2002	Martinon et al detect a caspase-activating complex called "The Inflammasome" which give the basics for the exact molecular mechanisms in which pyrin participates in the disease process	(Martinon et al., 2002)
2007	Papin et al detect that pyrin binds particular inflammasome components such as caspase-1 and interleukin-1B that was a great discovery to reveal the disease process at the molecular level	(Papin et al., 2007)

b. Articular attacks:

About 75% of the patients experience articular and joint pain. The three main manifestations are: an elevated fever in the first day, a bilateral fashion of attacks involving large joints of the leg and a gradual decrease in the symptoms after a peak in 24-48 hours (Shohat and Halpern, 2010). The attacks are commonly in the hip or knee but it can emerge to the ankle, shoulder, temporomandibular or sternoclavicular joints (Shohat and Halpern, 2011). As a result, arthritis, arthralgia and myalgia can occur (Ali et al., 2016).

c. Pleuritis:

Pleural attacks accompanied with high-peaking fever have been described in 10% of pediatric patients. Physical examination is nonspecific in young patients and is mainly characterized by unilateral chest pain that increases in inspiration, shortness of breath, febrile dyspnea and rapid shallow breathing (Tarantino et al., 2016).

d. Pericarditis:

Pericarditis is commonly seen with FMF, presenting usually as chest pain and an increase in ST segment of electrocardiogram. It is difficult to detect when accompanied with pleuritis (El Shanti et al., 2006; Okutur et al., 2008). Yet, massive pericardial effusions and cardiac tamponade have been reported requiring pericardiocentesis (Tunca et al., 2005; Ishak et al., 2006; Sanchez Ferrer et al., 2015).

e. Amyloidosis:

Amyloidosis is considered one of the powerful complications caused. It affects the kidney causing a large amyloid deposition in the tissues of this organ as abnormal, insoluble fibers. This accumulation results in nephrotic syndrome and it may lead to end-stage renal disease (ESRD) (Bilginer et al., 2011). Although the kidney is the most organ affected, serum amyloid A (SAA) can be accumulated in the gastrointestinal tract, the liver, the spleen, the thyroid and after a long period in the heart and testes as well (Ben-Chetrit and Levy, 1998; Lofty et al., 2016). The high risk of developing amyloidosis is when the patient does not have a rapid diagnosis after the disease onset and subsequently does not begin with the treatment (Cefle et al., 2005). Varan et al. showed that high CRP levels during the attack-free periods may be a strong risk factor for the development of amyloidosis in patients with FMF (Varan et al., 2019).

f. Sleep disturbances:

Poor sleep quality is common in adult FMF patients. Anxiety, depression and fatigue are more frequent in FMF patients than healthy individuals (Kucuksahin et al., 2017).

Makay et al. showed that sleep quality was negatively affected by the number of attacks. Patients with a higher number of attacks were noted to struggle in falling asleep (Makay et al., 2014). In fact, inflammation can contribute to mood disorders and sleep disturbance.

2.2. Rare Symptoms

In rare cases, the common symptoms are accompanied with protracted febrile myalgia, erysipelas-like erythema over the lower limbs, reduced fertility and vasculitides (Ostring and Singh-Grewal, 2016; Shohat and Halpern, 2011).

3. DIAGNOSIS OF FMF

Since FMF usually requires lifelong treatment, it is important to establish a timely, correct diagnosis. During attacks, there is a huge influx of sterile poly-mononuclear leukocytes to affected sites in the body. Therefore, inflammatory serological studies indicate increase in acute phase reactants such as C-reactive protein, fibrinogen, erythrocytes-sedimentation rate and increased white blood cell count with neutrophilia (Zadeh et al., 2011). Occasionally, the presentation is less typical and, molecular genetic testing may be helpful (Sonmez et al., 2016; Soriano and Manna, 2012).

3.1. Molecular Genetic Testing

Diagnostic molecular testing comprises different testing strategies (Booty et al., 2009). Targeted molecular testing for the 12 most common MEFV mutations (E148Q, P369S, F379L, M680I (G/ C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H). Example of Targeted Mutation Analysis: Familial Mediterranean fever strip assay. This particular assay is designed to detect the mutations by polymerase chain reaction and reverse hybridization (Ben-Chetrit and Touitou, 2009). Also, offering full sequence analysis of all the coding exons of the MEFV gene to assure accuracy (Zadeh et al., 2011).

3.2. Multiple Serum Cytokine Profiling to Identify Combinational Diagnostic Biomarkers in Attacks of Familial Mediterranean fever

Several studies showed that IL-6 increased in the serum during FMF attacks (Manukyan et al., 2008; Akcan et al., 2003; Gang et al., 1999). IL-6 is a main inflammatory cytokine and as a promising target in this disease. IL-1 signaling plays pathogenic roles in the development of auto inflammatory disease (Chung et al., 2009). On the other hand, IL-17 and IL-18 serum levels of FMF patients both in attack and in remission were significantly higher than those of healthy controls, as well as CXCL10, IL-12p40, and IFN- γ in addition to sCD54 levels, but not significantly higher than the levels of patients in remission. Elevated serum levels of IL-10 along with pro-inflammatory cytokines were reported in FMF patients in attack (Manukyan et al., 2008).

In addition, IL-12 serum level increased in patient in both remission and attacks (Ben-Zvi and Livneh, 2011; Erken et al., 2006).

4. MOLECULAR AND GENETICS

There is a wide number of MEFV mutations linked with FMF. Across all FMF patients, nearly around 80% of MEFV mutations are accounted for by E148Q, M680I, M694I, M694V, and V726A. The percentages for the particular mutation in a single mutation cases differ by the population under study (Aslan, 2011). The studies also indicate that individuals with 1 MEFV mutation exhibit symptoms that are often less severe than individuals with 2 mutations, and they also show higher levels of other inflammation markers than individuals with no mutations.

Studies are beginning to appear in the literature that attempt to identify the reasons that the typically recessive MEFV mutation begins to behave as if dominant, thereby causing the clinical symptoms of FMF (Touitou, 2013). The body evidence is suggesting that the environmental and epigenetic sources are important in triggering disease expression in patients with a single mutation (Jeru et al., 2013).

Recently, studies showed that a heterozygote state might also result in the disease. Mutations are located in MEFV as mentioned earlier and encode a protein called pyrin/marenostrin/TRIM20. Among more than 300 mutations in the MEFV gene are now the most common in classically affected populations. There are mutations in 6 of the 10 exon of the MEFV (1, 2,3,5,9, and 10), where the three hot spots mutations are on exon 2 and 10 (E148Q, E148V/ M694V, M694I, M694 del/ M680I (G/C), M680 (G/A), M680L). There are 29 known mutations (26 missense, 1 nonsense, 2 small deletions). Phenotypes ranges from mild (E148Q mutation is the mildest and least penetrant) to severe (genotype include 2 mutations in the gene codon 680 or 694) (Giaglis et al., 2007).

5. PYRIN PROTEIN

5.1. Pyrin Structure and Protein-protein Interaction

MEFV gene encodes for the protein called pyrin. It is composed of an N-terminal RING domain, B-box domain and a C-terminal coiled-coil domain where most mutations are found (Manukyan and Aminov, 2016). There are several interactions between pyrin and many other proteins and oligomers, Figure 1. For example, the PYD domain interacts with an adapter protein called apoptosis-associated speck-like protein (Richards et al., 2001).

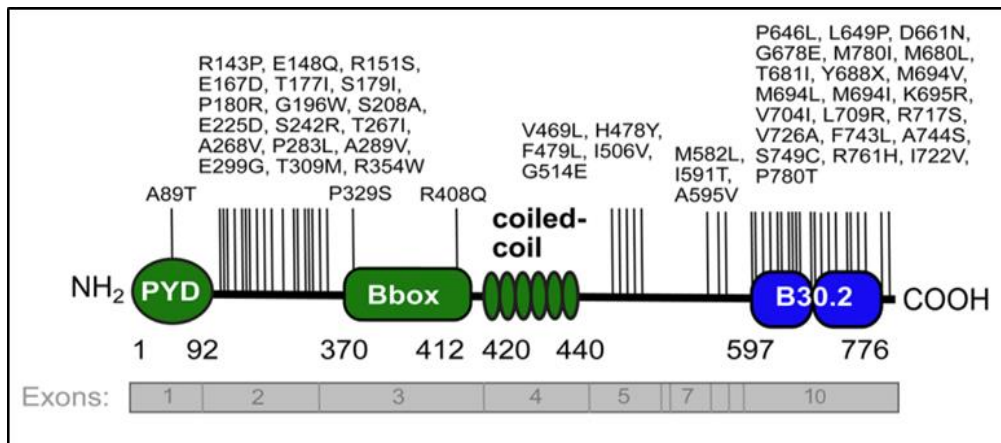


Fig.1: Schematic outline of pyrin structure ((Rosalie Heilig and Petr Broz, 2018)

5.2. Regulation of Innate Immunity by Pyrin

Through the PYD domain, pyrin regulates IL-1 β activation resulting in proinflammatory (Yu et al., 2006, Seshadri et al., 2007; Gavrilin et al., 2012) or anti-inflammatory (Chae et al., 2006; Papin et al., 2007; Hesker et al., 2012) effects. Most of the studies suggest that the NALP3 inflammasome complex has a significant impact in the pathogenesis of FMF (Papin et al., 2007; Omenetti et al., 2014).

5.3. Pyrin and Danger Signals

A new interaction of pyrin with the adaptor protein PSTPIP1 which regulates the cytoskeleton was confirmed by Waite et al (Waite et al., 2009). The correlation between pyrin and the cytoskeleton is confirmed by the efficiency of colchicine (Zemer et al., 1986). Table 2. Shows different drugs used in treatment of FMF.

5.4. Roles of Pyrin

Pyrin functions in inflammasome assembly (Vajjhala et al., 2014), by sensing intracellular danger signals (Kim et al., 2015; Dumas et al., 2014; Xu et al., 2014) and activation of mediators of inflammation by the inflammasome (IL-1 β , IL-18) (Kim et al., 2015; Chae et al., 2011). In addition, it plays a role in apoptosis (Richards et al., 2001; Martinon et al., 2001; Gumucio et al., 2002) in pyrin-cytoskeleton interactions (Waite et al., 2009) and in autophagy of innate immunity regulators (Kimura et al., 2015).

Table 2: Drugs used in the treatment of FMF.

Different drugs	Uses	Ref
Steroids or narcotics	Provide temporary relief of pain before definitive diagnosis	(Zadeh et al., 2011)
Nonsteroidal anti-inflammatory drugs	Treat fever and pain	(Zadeh et al., 2011)
Etanercept, infliximab, or adalimumab	Control FMF attacks such as chronic arthritis and sacroiliitis	(Bilgen et al., 2011)
Anakinra	Suppresses inflammation	(Grattagliano et al., 2014)
Colchicine	The mainstay of treatment since 1972. It increases the quality of life and prevents the development of amyloidosis and the recurrence of febrile attacks	(Goldfinger, 1972; Sonmez et al., 2016; Ozdogan and Ugurlu, 2019)
Tocilizumab	Controls the signs related to the attacks, and prevents the development of AA amyloidosis	(Ugurlu et al., 2017; Migita et al., 2018)
Canakinumab	Improves renal functions, reduces attacks, decreases the level of high-level laboratory findings associated with FMF and is an effective therapy to patients who are resistant to colchicine	(Yazilitas et al., 2018; Berdeli et al., 2019)

6. CONCLUSION

- This monogenic disease continues to be of interest to clinical and basic researchers.
- Experts have worked on compiling recommendations to guide physicians in the diagnosis, management, and treatment of FMF.
- Colchicine is the drug mostly recommended, and IL1-blockade is recently being considered. Further, molecular investigation is required.

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