Review

Knowledge About Familial Mediterranean Fever: A Literature Review

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Knowledge About Familial Mediterranean Fever: A Literature Review

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Abstract: Familial Mediterranean fever (FMF) is an uncommon genetic fault that results in persistent episodes of fever and inflammation in various parts of the body. FMF is caused by mutations in the MEFV gene, which codes for the inflammation-regulating protein pyrin. It affects mainly people of Mediterranean origin, but it can occur in any racial group. FMF symptoms often begin in childhood and range in intensity and frequency. The episodes range from a few hours to a few days and end spontaneously. The patients are often symptom-free in between bouts. However, some patients may experience side effects including amyloidosis, a dangerous disorder brought on by the buildup of an aberrant protein called amyloid in the organs, particularly the kidney. The diagnosis of FMF is based on the clinical criteria, the family history, and the genetic testing. The prescription of colchicine, a medication that prevents amyloidosis and lessens the frequency and intensity of episodes, is the standard therapy for FMF. Being a chronic illness, FMF needs frequent monitoring and commitment to therapy. With adequate care, most FMF patients may lead normal and productive lives.

Keywords: MEFV gene; FMF; colchicine

1. Introduction

Familial Mediterranean fever (FMF) is a chronic inflammatory disorder marked by fever and serositis flare-ups. The notable frequency or occurrence of the ailment within the Sephardic Jewish, Armenian, Turkish, and Arab populations has been extensively documented for several decades; but, in recent years, FMF has been detected in various other populations across the globe, albeit with significantly lower prevalence rates. Inadequate recognition or treatment of individuals may result in the pathogenesis of AA amyloidosis, which is a primary cause of death [1,2].

Familial Mediterranean has been referred to by various names including benign paroxysmal peritonitis, periodic fever, periodic amyloid syndrome, periodic peritonitis syndrome, Armenian syndrome, Riemann periodic disease, and Siegel-Cattan-Mamou syndrome. The term "familial Mediterranean fever" was coined by Heller in 1955 and has since gained widespread global acceptance [3].

2. Global Prevalence of FMF:

FMF is widely regarded as the most typical monogenic auto-inflammatory disorder, exhibiting a prevalence rate of 1/1073 among the Turkish population, and a higher rate of 1/395 in central Anatolia. The carrier frequency of the aforementioned genetic feature is discovered to be 1/5 among Turkish and North African Jewish people. 1/7 among Armenians, and 1/11 among Ashkenazi Jews

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[4]. A significant number of instances have been identified among Arab populations in Jordan, Lebanon, and Syria. The spread of FMF illness has gone worldwide and is now commonplace in several nations, including France, Germany, Italy, Spain, the United States, Australia, and Japan [5–7].

3. Familial Mediterranean Fever: Insights from Molecular Genetics

A protein variation called pyrin or marenostrin is encoded by the MEFV gene, which serves as a critical participant in the immune system that develops naturally and is a constituent of the inflammasome. This results in an augmented inflammatory reaction through unregulated interleukin-1 synthesis [8].

The MEFV gene mutation is found on chromosome 16's short arm and consists of 10 exons. Exons 10 and 2 encode the most prevalent genetic alterations, the causative agents that account for over 85% of FMF cases in the Mediterranean basin. Thus far, Infevers, an online database for mutations implicated in auto-inflammatory diseases, has identified 397 sequence variants for the MEFV gene [9,10].

The autosomal recessive inheritance pattern of Familial Mediterranean Fever (FMF) underscores the importance of identifying two mutations in individuals presenting with clinical FMF. However, empirical research has indicated the absence of a second allele in nearly 30% of individuals exhibiting a familial Mediterranean Fever (FMF) phenotype. Scientists are curious about the potential causes of autosomal recessive diseases in which a second mutation is not present [11]. The influence of environmental factors on the aforementioned parameters is also crucial in the happenstance of the symptomatology of disease in people with a single genetic mutation [3].

The majority of mutations are attributed to point mutations, which are also referred to as missense mutations. The mutations E148Q, M680I, M694V, M694I, and V726A have been associated with over 80% of (FMF) cases in the Middle East [12]. Table 1 indicates that there may be variations in the frequency and prevalence of mutations observed in the MEFV gene across ethnically distinct peoples [13].

4. Pathogenesis:

The pathogenesis of FMF is significantly influenced by the involvement of Interleukin-1 beta (IL-1β), and it is plausible that mutations associated with FMF lead to an upsurge in the production of IL-1β. The nature of causative MEFV mutations, whether of the loss-of-function or gain-of-function variety, has remained ambiguous [14,15].

Table 1. MEFV gene mutation frequency in various populations.

The most common MEFV gene variants identified in distinct ethnic groups
Turks M694V, M680I, V726A, E148Q
Armenians M694V, M680I, V726A, E148Q
Jews North African M694V, E148Q
Iraq V726A, M694V, E148Q, M680I
Ashkenazi E148Q, V726A

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Arabs	
V726A, M680I, M694V, M694I, E148Q	

Papin and colleagues offered evidence in favor of the loss of function model by exhibiting an In contrast, Chae and colleagues presented proof in favor of the gain of function hypothesis by demonstrating that knock-in mice carrying B30.2 mutations associated with (MEFV exon 10 mutations) exhibited a pronounced spontaneous inflammatory phenotype, whereas pyrin-deficient mice did not. However, it should be noted that this issue remains a subject of controversy [16]. According to recent research, pyrin can detect bacterial modifications in Rho GTPases, and cause the activation of inflammasomes and subsequent elevation of IL-1b levels. Since Pyrin is a downstream component of the actin cytoskeleton pathway, Pyrin likely interacts with a Rho effector kinase to recognize Rho modifications [17].

5. The Relationship Between Phenotype and Genotype:

Researchers have posited that a correlation exists between the symptoms of Familial Mediterranean Fever (FMF) and an individual's genotype. As per certain researchers, individuals who exhibit homozygosity for the M694V mutation manifest a disease course that is comparatively more severe. When viewed from this perspective, it has been reported that homozygous M694V cases exhibit a higher frequency of the disease's most severe complication, amyloidosis. Studies examining the incidence rate of fever and stomach ache, which are considered crucial FMF clinical signs, have yielded inconsistent results with some studies failing to establish a correlation [13,18]. It has been determined by other researchers that the aforementioned symptoms exhibit a higher incidence rate among individuals possessing an M694V or M680I genotype. In relation to the age at which the disease first manifests, some research suggests that the illness manifests at a precursory state in individuals carrying the M694V mutation, while other studies indicate that the disease emerges later in homozygous M694V patients. Nevertheless, several studies have failed to establish a correlation between genotype and the age of disease onset. There is a significant difference between studies that examine the relationship between phenotype and genotype. The consensus among researchers suggests that the severity of the disease is heightened among individuals who have the M694V mutation and are homozygous for it [19].

6. Clinical Presentations:

The onset of FMF attacks occurs in approximately 90% of patients before reaching 20 years of age. The mean age at which symptoms first appear falls within the range of 3 to 9 years. Although premature onset is not an exceptional occurrence, the manifestation of attacks throughout the first year of an individual's life is comparatively infrequent in comparison to other autoinflammatory diseases (AIDs), such as mevalonate kinase deficiency (MKD). Although infrequent, the occurrence of onset after the age of 40 has been noted in the initial reports. The occurrence of late-onset FMF appears to be more widespread in males and is linked to a less severe manifestation of the disease, which can be effectively treated with a lower dosage of colchicine. Several FMF series exhibit a slight male preponderance, approximately 1.22 males for every female [20,21].

6.1. Attacks:

FMF is the most common among periodic fever syndromes; however, the episodes are not characterized by periodicity, but rather by recurrence. The frequency of attacks among untreated patients exhibits a range from monthly occurrences to sporadic episodes throughout the year. A classical attack is typified by pyrexia and serositis, presenting as abdominal discomfort and or thoracic discomfort and or arthralgia and edema. The manifestation of an erythematous rash is a prevalent characteristic of the ailment. Episodes of attacks are typically of a finite duration, ranging

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from one to four days [3]. The complexity of the clinical presentation may be further compounded by the co-occurrence of vasculitis, sacroiliitis, or neurological manifestations. Several factors that can trigger an attack have been documented, including exposure to cold, emotional stress, and prolonged periods of standing or physical activity [14,15]. The primary clinical presentation of FMF is fever, feverless attacks being a rare occurrence, referred to as isolated fever attacks. In instances of severe attacks, the temperature may elevate to 39-40 degrees Celsius, whereas mild episodes may present with low-grade fever. In most cases, the duration of the fever is shorter than that of the accompanying serositis [22].

6.2. Peritonitis:

The prevailing attack type of peritonitis (FMF) is an abdominal attack. These symptoms are commonly linked with rebound tenderness, muscular stiffness, and reduced gastrointestinal motility. FMF accounts for 5% of the cases referred to an emergency department for abdominal pain. Around 33% of patients receive surgical interventions, such as appendectomy or cholecystectomy. Severe attacks of FMF may be provoked by peritoneal irritation resulting from surgical or diagnostic procedures. The recurrence of peritonitis has the potential to result in ileus or infertility, a phenomenon that was more prevalent before the advent of colchicine [3,23].

6.3. Pleural Involvement:

Pleural involvement is known to cause chest pain in approximately 30-50% of patients. Typically, it is a unilateral condition that hinders the ability to take deep breaths. The sensation of discomfort has the potential to spread to the abdominal region, dorsal area, or upper extremity. Concomitant manifestation of pleuritis with peritonitis is a common occurrence, while its co-occurrence with pericarditis is infrequent. The occurrence of pleural adhesions as a result of recurrent pleuritis is infrequent [24].

6.4. Synovial Attack:

The prevalence of synovial attacks is high among North African Jews, with a notable incidence among the pediatric population. The condition is characterized by repeated occurrences of non-deforming, mono, or oligo articular inflammation, primarily affecting articulations of the lower extremities. The prevalence of the aforementioned condition is higher among North African Jewish populations and is linked to the M694V genetic mutation, resulting in a severe manifestation of the disease and Amyloidosis may occur. The range of the involvement of joints in FMF spans from synovitis which is acute and self-limited to arthritis which is chronic and deforming. The most prevalent and prototypical manifestation is ephemeral monoarthritis affecting the ankle or the knee joint. Approximately 50% of these attacks exhibit the manifestation of an erythematous rash on the affected joint. Significant accumulations of fluid may be identified, particularly in the knee joints [3,25].

6.5. Erysipelas-like Erythema (ELE):

This represents the most prevalent cutaneous manifestation of Familial Mediterranean Fever. The aforementioned are characterized as sensitive, crimson, inflamed growths typically situated along the leg regions, ankle joint, and upper surface of the foot, occasionally accompanied by elevated body temperature [3].

6.6. Myalgia:

Patients with fibromyalgia frequently report experiencing myalgia, a symptom that exerts a substantial influence on their overall well-being. Episodes of acute inflammation characterized by myalgia and protracted febrile myalgia (PFM) are infrequent occurrences. The occurrence of PFM is associated with a significantly elevated acute phase response, the presence of the M694V genotype,

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and a notably severe disease trajectory. The efficacy of colchicine in managing PFM is limited, and the standard approach involves administering elevated dosages of corticosteroids or anti-IL-1b agents [13,26].

6.7. Amyloidosis:

The most severe and potentially fatal manifestation of Familial Mediterranean Fever (FMF) is amyloid nephropathy, which encompasses a range of conditions such as Nephrotic syndrome, renal vein thrombosis, and renal failure. In the absence of medical intervention, amyloidosis frequently culminates in renal insufficiency, representing the primary enduring health hazard in FMF. The efficacy of colchicine in the prevention, delay, or reversal of renal complications associated with amyloidosis has been demonstrated. Patients with advanced kidney disease may require dialysis or renal transplant as a necessary course of treatment [27].

7. Familial Mediterranean Fever: A Diagnosis

Is a condition that presents with non-specific symptoms, making it challenging to differentiate from other disorders that may manifest with similar clinical features. The identification of FMF necessitates a heightened level of suspicion and relies on the clinical criteria of a transient, reversible serosal attack and affirmative familial medical background. The sole approach to ensure an accurate diagnosis of familial Mediterranean fever is through the direct examination of the MEFV gene for mutations. Confirmation of FMF diagnosis is established if the frequency or occurrence of attacks is reduced or eliminated by the administration of colchicine [28,29]. Table 2 indicates the Criteria for identifying familial Mediterranean fever [30].

8. Familial Mediterranean Fever Laboratory Tests:

FMF is distinguished by increased acute phase markers such as ESR, fibrinogen, and serum amyloid A (SAA). CRP levels rise throughout episodes, while albumin remains unchanged, in the inter-episode period, CRP levels are higher than normal, while SAA levels are high. Patients serving as controls who had a mutation in the MEFV gene showed elevated levels of acute phase proteins greater than in those who are healthy and have no mutation. The levels of IL-6, IL-1, autoantibody frequencies, bilirubin levels, transaminase measurements, urinalysis, and occult blood in feces in patients with FMF episodes were all reported to increase during episodes [31].

9. The Management of Familial Mediterranean Fever:

Treatment aims to minimize morbidity and avoid illness consequences. At this phase, FMF is treated with colchicine, a neutrophil-suppressive drug. Studies show that 75% of individuals with FMF had complete symptom remission and around 95% exhibited considerable improvement with colchicine. Because colchicine is extremely powerful at avoiding FMF attacks and the development of amyloidosis, the crucial element of medical treatment is making an accurate diagnosis and initiating therapy. Colchicine is an efficient treatment for FMF, administered with 0.6mg bid in adults and 0.02-0.03 mg/kg/24 hr in children [32,33].

9.1. Colchicine and Pregnancy:

FMF has been linked to an increased likelihood of miscarriage and infertility, however, investigations have shown that all newborns are in perfect health. Colchicine treatment has never been linked to an increased risk of malformations in babies born to women who are taking it, so it is recommended for pregnant patients with FMF. The safety of colchicine in nursing mothers is low and similar to those in serum [34,35].

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9.2. Colchicine Interference:

Colchicine is an alkaloid that may influence mitosis and other microtubule-dependent activities by interfering with microtubule formation. Colchicine and any metabolites that it produces are eliminated via the urine and biliary systems, making it a generally secure and efficient drug in people with normal kidney and liver function when administered in proper doses. Early detection of colchicine toxicity is critical since it may be lethal if left undetected and untreated [36].

Table 2. Criteria for diagnosing familial Mediterranean fever.

Major Criteria	Minor Criteria
A common occurrence of attacks 1. Peritonitis (generalized) 2.Pleuritis (unilateral) or pericarditis 3. Monarthritis (hip, knee, ankle) 4. Fever 5. Abdominal attack with incomplete presentation.	Partial attacks that entail one or more of the subsequent locations: 1. Chest 2. Joint 3. Leg ache from exertion 4. Colchicine reaction positive

10. Conclusion

Familial Mediterranean fever is a hereditary illness characterized by recurring fever and inflammation in the body. Individuals with this illness must collaborate closely with healthcare providers to control symptoms and avoid consequences. While it has no known cure, there are treatments available to help manage symptoms and improve quality of life. In the future, ongoing research into the disease's underlying genetic and inflammatory pathways may eventually lead to new and more effective therapies.

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Conflicts of Interest: The authors declare that they have no competing interests.

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