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AİLESEL AKDENİZ ATEŞİ HAKKINDA BİLİNENLER: LİTERATÜR TARAMASI

Hüseyin Erdal[1], Recep Eröz [1]

[1] Aksaray University, Faculty of Medicine, Department of Medical Genetics, Aksaray, Turkey

Özet

Kalıtsal otoinflamatuar hastalıkların en sık görüleni Ailevi Akdeniz Ateşidir (AAA). Genellikle, AAA bağışıklık düzenlenmesinde yardımcı bir protein olan ve MEFV geninin fonksiyon mutasyonlarının kazanılmasından meydana gelmektedir. Son yıllarda, gelişen teknolojik gelişmeler ile birlikte AAA tanısında, genetik testlerde ve tedavi uygulamalarında önemli ilerlemeler görülmektedir. Özellikle, yeni nesil dizileme uygulamaları klinik açıdan önemli olan gen varyantlarının ortaya çıkmasına neden olmuştur. AAA, klinik olarak kısa ataklarla karakterize bir hastalık olarak görülse de, yapılan çalışmalarda kronik inflamatuar durum ile ilişkisi gösterilmiştir. AAA tedavisinde erken teşhis ve tedaviye olumlu yanıt hastaların iyileşme sürecinde oldukça önemlidir. Son yıllarda AAA hastalığı üzerine yapılan araştırmalar gittikçe artmaktadır. Bu derlemede, AAA üzerine son dönemde yapılmış olan çalışmaların ve elde edilen bulguların değerlendirilmesi amaçlanmıştır.

Anahtar Kelimeler: FMF, *MEFV*, Ailevi Akdeniz Ateşi

THE KNOWN ABOUT FAMILIAL MEDITERRANEAN FEVER: LITERATURE REVIEW

Abstract

The most common hereditary autoinflammatory disease is Familial Mediterranean Fever (FMF). Generally, FMF consists of acquiring function mutations of the MEFV gene, which is an auxiliary protein in immune regulation. In recent years, important advances have been seen in the diagnosis of FMF, genetic tests and treatment practices, together with the developing technological developments. In particular, new generation sequencing applications have led to the emergence of clinically important gene variants. Although FMF is clinically seen as a disease characterized by short attacks, studies have shown its relationship with a chronic inflammatory state. In the treatment of FMF, early diagnosis and positive response to treatment are very important in the recovery process of patients. In recent years, research on FMF has been increasing. In this review, it is aimed to evaluate the recent studies on FMF and the findings obtained.

Key Words: FMF, MEFV, Familial Mediterranean Fever

Sorumlu Yazar/Corresponding Author: Hüseyin Erdal , Aksaray University, Faculty of Medicine, Department of Medical Genetics, Aksaray, Turkey. E-mail: herdalyfa@gmail.com

INTRODUCTION

Familial Mediterranean Fever (FMF) is the most common inherited autoinflammatory disease in the world. It has been shown that the gene causing FMF disease is the *MEFV* gene, localized in the short arm (16p13.3 locus) of Chromosome 16 and consists of 10 exons. FMF results from the acquisition of functional mutations in the *MEFV* gene that encodes a protein called pyrin, which has regulatory functions on the innate immune system. (Tufan & Lachmann, 2020). The "pyrin" protein consists of 781 amino acids, which is the product of the *MEFV* gene plays an important role in inflammatory reactions. Mutations in *MEFV* may result in less active pyrin formation (Masters, Simon, Aksentijevich, & Kastner, 2009). First described in 1945 as "benign paroxysmal peritonitis" (El-Shanti, Majeed, & El-Khateeb, 2006). The typical phenotype of FMF includes self-limiting fever and inflammatory attacks of polyserositis, arthritis, and dermal manifestations with a high acute phase response (El Hasbani, Jawad, & Uthman, 2019). Although FMF is known to affect societies such as Arabs, Armenians, Turks, Greeks, Italians, Persians and Jews in the Mediterranean region and FMF is seen worldwide due to increased immigration and travel, especially with the 20th century (Ben-Chetrit & Touitou, 2009; Cakirca et al., 2018). Turkey is one of the countries with the highest number of FMF patients in the world. It is estimated that there are more than 100,000 FMF patients in Turkey, as the prevalence of FMF is about 1:400 to 1:1,000 (highest in Anatolian regions) and the population is about 82 million ("Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study," 2005; Tripathy, Sinha, & Nityanand, 2004). The duration of a typical FMF attack is approximately 3 days. The frequency of occurrence varies from once a week to several times a year. There are multiple damaging complications of FMF, one of which is the development of serum amyloid A (SAA) amyloidosis, which affects other organs, primarily the kidneys (Ben-Chetrit & Touitou, 2009). Amyloidosis is one of the most important causes of renal failure and is especially associated with the death of young adult patients. For this reason, it is inevitable that kidney failure will develop to a large extent in individuals with FMF disease if amyloidosis is not treated. Studies have shown that 7-13% of Turkish FMF patients have amyloidosis (Eroz, Dogan, & Kocabay, 2016).

MATERIALS AND METHODS

The Embase, MEDLINE, Web of Science Core Collection, and Google Scholar databases were used for the literature search. As a keyword; The ‘’FMF, *MEFV*, Familial Mediterranean Fever, Amyloidosis, Colchicine’’ words were used.

DISCUSSION AND RESULTS

In the literature, studies have shown high levels of inflammation with high levels of proinflammatory cytokines and increased acute phase reactants in FMF patients during attack periods (Baykal et al., 2003; Cakirca et al., 2018). Studies have shown that oxidative stress increases in FMF patients (Guzel et al., 2012; Ediz et al., 2011). Oxidative stress (OS) occurs as a result of the increase in free radical production during inflammation and the resulting decrease in antioxidant defense mechanisms and causes damage to macromolecules such as lipid, protein and nucleic acid in the organism (Ozcan, Erdal, & Yonden, 2015; Özcan et al., 2015; Erdal, Ozcan, Turgut, Neselioğlu & Erel, 2022). Markers of lipid peroxidation (eg, conjugated diene and malondialdehyde), protein oxidation (eg, protein carbonyl) and DNA oxidation, and thiol-disulfide balance are used to determine oxidative damage (Erdal, Ciftciler, Tuncer, & Ozcan, 2022; Ozcan et al., 2018; Özcan etal., 2015; Erdal, et al., 2019; Gunes, et al., 2020; Erdal et al., 2022). Therefore, these markers play an important role in the etiopathogenesis of many diseases, including FMF. FMF symptoms usually begin before the age of 20. The clinical phenotype is usually more severe in patients whose attacks begin at an early age.

These patients have recurrent episodes of fever, serositis, arthritis, and high levels of inflammatory reactants. (Maggio & Corsello, 2020). FMF attacks are repeated in the presence of infection, exposure to stress, menstrual bleeding, exposure to cold and consumption of foods rich in fat. In these patients, fever is seen as a typical symptom in more than 96% of inflammatory attacks, with a frequently elevated body temperature between 38 and 40°C, and chills before fever are observed in 25% of them (Maggio & Corsello, 2020; Manna & Rigante, 2019). The length of self-limiting episodes lasting from 1 to 4 days may have mild prodromal symptoms (myalgia, arthralgia, lumbar spine pain, headache, dyspnea, nausea, arthralgia, asthenia, restlessness) lasting approximately 17 hours. Clinically, we can distinguish 3 phenotypes of FMF as type1, type 2 and type 3.

Type 1: Patients with acute episodes of fever, painful serositis, and classic symptoms of arthritis

Type 2: Patients with renal amyloidosis without FMF symptoms and without fever attacks

Type 3: Patients with two *MEFV* gene mutations and without fever, other FMF symptoms, or amyloidosis.

The most current criteria for the diagnosis of FMF are Tel Hashomer clinical criteria. (Shohat & Halpern, 2011). The main symptoms are fever, abdominal pain, chest pain, skin rash and joint pain. Criteria suggesting a diagnosis of FMF in individuals with recurrent monoarthritis are high fever, positive response to colchicine, a history of FMF in siblings and other family members, and a suitable genotype (Lidar et al., 2005; Shohat & Halpern, 2011). Colchicine is the first step in the treatment of patients with recurrent attacks, even if there is no fever in the treatment of FMF, and it has been used in the treatment of FMF since 1972 (Migita et al., 2018). Colchicine controls the attacks that occur in the patient and prevents the development of amyloidosis. Therefore, as soon as the clinical diagnosis is made, treatment of colchicine is started in individuals with symptoms. The daily drug dosage is 0.5–1 mg/day, and a therapeutic trial of at least 3–6 months is useful to determine the true response to the drug. (Maggio & Corsello, 2020). If inflammation persists despite good adherence to treatment, the dose can be increased gradually to 2 μg/day in children and up to 3 μmg/day in adults, by carefully monitoring the side effects. The severity of the disease and the patient's tolerance for recurrence of symptoms are essential elements in guiding the physician in obtaining a personalized dose of colchicine. Colchicine is less effective in controlling myalgia and arthritis, requiring the addition of non-steroidal anti-inflammatory drugs or corticosteroids. (Cerquaglia et al., 2005; Maggio & Corsello, 2020; Migita & Agematsu, 2011).

In addition to diagnosis and detection of rare diseases and variant such as a rare cause of delayed puberty and primary amenorrhea due to 17α-hydroxylase enzyme deficiency (Bestas et al., 2022), splicing variant in PSEN1 gene with a rare condition of the Alzheimer's Disease with spastic paraparesis (Dogan, Eroz, Tecellioglu et al., 2022), maturity-onset diabetes of the young (Dogan, Eroz, Bolu, et al., 2022), White-Sutton syndrome with hot water epilepsy (Turay & Eroz, 2021), an ultra-rare condition of *ELP2*-related neurodevelopmental disorder (Dogan, Terali, Eroz, Demirci, & Kocabay, 2021), Boucher-Neuhauser syndrome (Dogan, Eroz, & Ozturk, 2021), novel *GNPTG* variants causing mucolipidosis III gamma phenotypes (Dogan, Eroz, Terali, Gezdirici, & Bolu, 2021), a novel pathogenic variant in the *AGTPBP1* gene (Turay, Eroz, & Basak, 2021), novel *FBN1* variants (Gezdirici et al., 2021), Glucokinase Mutations Associated Maturity-Onset Diabetes (Bolu, Eroz, Dogan, Arslanoglu, & Dundar, 2020), novel mutation in the *DDB2* gene of patients with xeroderma pigmentosum group-E

(Karagun et al., 2020), novel pathogenic variant of Alport syndrome (Eroz, Damar, & Kilicaslan, 2020), novel homozygous deletion mutation in the glucokinase gene (Bolu, Eroz, Dogan, Arslanoglu, Uzun, et al., 2020), patients with Myotonia Congenita (I. H. Damar & Eroz, 2019), Megalencephalic Leukoencephalopathy (Soysal et al., 2015), EEC syndrome (Okur et al., 2012), novel variant in tuberous sclerosis (Kurt, Dogan & Eroz, 2021; Kurt, Eroz, Dogan, 2022), the detection and discrimination of pathogenic variants in comman diseases such as FMF can be done by whole exom sequencing. For example, the novel c.334-335 DelG P.Glu112fs variation in exon 2 (Eroz, Doğan, & Yuce, 2016), novel K447M(P.Lys447Met, C.1340 A>T) variation in exon 4 (Eroz, Dogan, & Kocabay, 2016), and rare A89T (p. Ala89Thr, c.265G>A) variation (Eroz, Dogan, Yuce, Kocabay, & Yuksel, 2016) , rare E167D variation (Eroz, Yuce, & Koksal, 2019), rare 761_764dupCCGC p.Asn256Argfs variation (Eroz, Dogan, Huseyin, & Ozmerdivenli, 2016), rare S288Y(P.Ser863Tyr, C.863 C>A) variation (Dogan, Kocabay, Ozmerdivenli, & Eroz, 2016) were detected in the disease.

For the analysis of FMF, the main known tests are widely used. Sanger sequencing, one of these tests, is currently the recommended initial molecular test for FMF. This method is very suitable for low-throughput laboratories where the next-generation sequencing (NGS) approach would not be profitable (Ozen, 2021; Shinar et al., 2020). The first NGS device was introduced to researchers in 2005 and has led to significant developments in the field of molecular genetics since this date (Dogan, Eroz, Yuce, & Ozmerdivenli, 2017). The NGS method is based on the creation of a library from a large number of DNA fragments resulting from the cutting of DNA through enzymatic reactions and the duplication of the DNA fragments that make up this library. With this process, parallel sequencing and simultaneous sequencing of large numbers of small DNA fragments is performed. In this way, it is possible to read the bases on the genome more than once and to detect the variations correctly. (Buermans & den Dunnen, 2014; Dogan, Eroz, Yuce, & Ozmerdivenli, 2017). An important advantage of sequence data in NGS is the quality, robustness and low noise of the obtained data. Success of NGS requires expertise in both laboratory and bioinformatics fields in order to interpret high-quality data correctly

Molecular diagnosis of patients with FMF can be made either by testing the five most frequently mutations detected in patients with AAA (p.Met694Val, p.Met694Ile, p.Val726Ala, p.Met680IleGC and p.Glu148Gln) or by sequencing of the 10 exons of the MEFV gene to detect the additional mutations in the related gene. In most individuals with

classic AAA, analysis of five common mutations (targeted mutation analysis) confirms the diagnosis. However, by expanding the panel of tested mutations to include an additional five variants (p.Arg761His, p.Ala744Ser, p.Lys695Arg, p.Met680IleGA and p.Pro369Ser), it can be determined at no extra cost whether it has been missed. Additional sequencing analysis may be considered in individuals with non-classical FMF or mild clinical presentation. (Migita & Agematsu, 2011; Shohat & Halpern, 2011). There are nine pathogenic variants (M694 V, M694I, M680I, V726A, R761H, A744S, I692del, E167D and T267I) of FMF. Other variants whose significance is not fully known are; E148Q, K695R, P369S, F479 L and I591T (El Hasbani, Jawad, & Uthman, 2019). M694V is the most common mutation in Eastern Mediterranean populations, although less common among Arabs (Majeed, El-Shanti, Al-Khateeb, & Rabaiha, 2002). Since M694V is associated with a severe disease phenotype, patients with homozygous M694V variation are considered to be at high risk for early disease. Baruk et al. showed that the frequency of M694 V homozygosity may be associated with non-response to colchicine (Barut et al., 2018).

Eroz et al. reported a novel single base mutation K447M (p.Lys447Met, c.1340 A>T) that causes a Pyrin/Marenostrin protein mutated in the coding region of the *MEFV* gene. In the study, where three variants have been reported in exon 4 so far, K447M (p.Lys447Met, c.1340 A>T) was shown to be the novel and firstly identified mutation in exon 4 of the *MEFV* gene. It was stated in the study that the relevant mutation would provide important information for future studies about FMF pathogenesis and genotype-phenotype association studies (Eroz et al., 2016).

Eroz et al., detected a 761_764dupCCGC (p.Asn256Argfs70,c.761_764dupCCGC) duplication mutation in the 2nd exon of the MEFV gene and they reported that it would provide important contributions to the pathogenesis of AAA in a different study conducted in FMF patients. (Eroz et al., 2016). Dogan et al. reported that a rare single-base S288Y (p.Ser863Tyr, c.863 C>A) mutation was identified in the 2nd exon region of the *MEFV* gene, and they reported that the single base change mutation shown would make a significant contribution to future studies on FMF (Dogan, Kocabay, Gun , Ozmerdivenli, & Eroz, 2016). In the study of Damar et al. showed that while there was no cardiovascular involvement in FMF patients with K447M mutation carriers, FMF patients with M6694V and R202Q compound mutation carriers were at risk for cardiovascular involvement and they reported that regular cardiological follow-ups were important in their study on cardiac involvement in FMF patients (Damar et al., 2019).

The exact understanding of both the contribution of the specific variant to clinical findings of FMF and genotype-phenotype correlation are important (Dundar et al., 2022). It was reported that a case with with Klippel-Feil Syndrome(KFS), Bilateral Sprengel Deformity, Congenital Unilateral Renal Agenesis and a pathogenic M680I(G>C) variant in the MEFV gene should be regularly followed for kidney failure and avoid from heavy exercise because the neurological deficits can be seen after minor trauma in cases with KFS during her life for amyloidosis risk (Kaya, Kabaklıoglu, & Eroz, 2021; Eroz, Dogan, Semih, & Huseyin, 2017). Also it was reported that because the FMF patients with chest pain and at least one *MEFV* gene variant have increased risk for cardiac problems, These patients should be routinely followed up for cardiac problems (Damar & Eroz, 2021).

CONCLUSION

The FMF patients have difficulty in doing their daily activities due to recurrent fever, abdominal pain, joint pain, serositis, arthritis and high level of inflammatory reactant attacks, risk of developing amyloidosis and cardiac risk. For this reason, it is important to diagnose the disease as early as possible and to apply appropriate treatment options in individuals with clinical symptoms in order to reduce the risk of developing amyloidosis and cardiac problems, as well as enabling the patient to perform daily vital activities and sports activities more comfortably and regularly. We think that this review will make important contributions to the current subject.

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