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Comorbidity Profile of Familial Mediterranean Fever Patients Varies by Treatments

Ailevi Akdeniz Ateşi Hastalarının Tedavilere Göre Değişen Komorbidite Profili

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Comorbidity Profile of Familial Mediterranean Fever Patients Varies by Treatments

ABSTRACT

Objective: Comorbidities may have an impact on the patient's quality of life and even survival. Treatment resistance in Familial Mediterranean Fever (FMF) may indirectly indicate severe disease, with inflammation-related comorbidities increasing as severity rises. In the literature, there are no sufficient studies regarding comorbidities in FMF patients. In this study, we aimed to evaluate the comorbid conditions of patients according to FMF treatment steps.

Material and Method: We retrospectively reviewed 740 patients with FMF treated at our rheumatology clinic between May 2019 and March 2024. Patient characteristics, comorbidities, and FMF treatments of patients were evaluated. Patients were grouped according to their FMF treatment: coated colchicine, compressed colchicine, and IL-1 inhibition. Patients received treatments aligned with their disease activity, in accordance with current reimbursement guidelines.

Results: The mean age (SD) of FMF patients was 40.7 (13.3) and 62.4% were female. Of the 44.7% all patients had at least one comorbidity. The three most common comorbidities are hypertension (20%), hyperlipidemia (7%), and depression (6.8%). The initial coated colchicine treatment was changed in a total of 24.5% to compressed colchicine, further step up was done in 13.2% patients to IL-1 inhibition. Hypertension and chronic kidney disease were more common in patients under IL-1 inhibitor treatment.

Conclusion: Our retrospective analysis shows that FMF patients, especially those in the IL-1 inhibitor group, frequently experience comorbidities like hypertension, hyperlipidemia, and depression, even though these patients are younger, suggesting a potential link to severe disease. A comprehensive evaluation of comorbidities, especially in severe disease, is essential to prevent complications, and improve quality of life.

Keywords: Colchicine, comorbidity, Familial Mediterranean Fever, hypertension.

ÖZET

Amaç: Komorbiditelerin hastanın yaşam kalitesi ve hatta sağkalımı üzerinde etkisi olabilir. Ailevi Akdeniz Ateşi (AAA) hastalarında tedaviye direnç/başarısızlık, şiddetli hastalığın dolaylı bir göstergesi olabilir. AAA hastalık şiddeti arttıkça, inflamasyon ve hasara bağlı komorbiditeler de artabilir. Literatürde AAA hastalarında, özellikle de tedaviye dirençli gruptaki erişkin hastalarda komorbiditelere ilişkin yeterli çalışma bulunmamaktadır. Bu çalışmada, AAA tedavi basamaklarına göre hastaların komorbid durumlarının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Mayıs 2019 ile Mart 2024 tarihleri arasında romatoloji kliniğimizde tedavi edilen 740 AAA hastası retrospektif olarak incelendi. Hastaların demografik özellikleri, komorbiditeleri, ailede AAA öyküsü ve AAA tedavileri değerlendirildi. Hastalar AAA tedavilerine göre kaplanmış kolşisin, sıkıştırılmış kolşisin ve IL-1 inhibitörü olmak üzere 3 gruba ayrıldı. Hastalar, mevcut geri ödeme kılavuzlarına uygun olarak hastalık aktiviteleri ile uyumlu tedaviler almıştır.

Bulgular: AAA hastalarının ortalama yaşı (SD) 40,7 (13,3) ve %62,4'ü kadındı. Hastaların %44,7'sinde en az bir komorbidite vardı. En sık görülen üç komorbidite hipertansiyon (%20), hiperlipidemi (%7) ve depresyondur (%6,8). Başlangıçtaki kaplanmış kolşisin tedavisi toplam %24,5 hastada sıkıştırılmış kolşisin olarak değiştirilmiş, %13,2 hastada ise IL-1 inhibisyonuna geçilmiştir. IL-1 inhibitörü tedavisi gören hastalarda hipertansiyon ve kronik böbrek hastalığı daha yaygındır.

Sonuç: Retrospektif analizimiz, AAA hastalarının, özellikle IL-1 inhibitörü grubundakilerin, daha genç olmalarına rağmen, hipertansiyon, hiperlipidemi ve depresyon gibi komorbiditeleri sıklıkla yaşadığını göstermektedir ve bu da şiddetli hastalık ve kronik inflamasyon arasında potansiyel bir bağlantı olduğunu düşündürmektedir. Özellikle şiddetli hastalığı olanlarda komorbiditelerin kapsamlı bir şekilde değerlendirilmesi, komplikasyonları önlemek ve yaşam kalitesini artırmak için gereklidir.

Anahtar Sözcükler: Ailevi akdeniz ateşi, hipertansiyon, kolşisin, komorbidite.

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory disorder marked by recurrent episodes of fever and serositis (1). It is linked to mutations in the MEFV gene, following an autosomal recessive inheritance pattern, with common mutations including M680I, M694V, and V726A (2).

Colchicine is the primary treatment; however 5-15% of patients are resistant or intolerant to it (3). In patients resistant or intolerant to colchicine, IL-1 inhibitors are the next line of approved treatments. However, in specific cases, other treatments such as tumor necrosis factor inhibitors for those with chronic arthritis and IL-6 inhibitors for those with amyloidosis can be used (4,5). There are differing opinions on the use of IL-1 antagonists in FMF treatment, with some suggesting they can be administered either continuously or on-demand, depending on the patient's clinical presentation (6). Recent studies have investigated the efficacy of different colchicine preparations in FMF treatment (7). Currently, colchicine preparations are divided into compressed and coated (sugar coated). The greater effectiveness of compressed colchicine is attributed to its different pharmacokinetic properties compared to sugar coated tablets (8). Compressed colchicine also improved treatment response in patients who were resistant or intolerant to coated colchicine (9). These findings suggest that compressed colchicine tablets may be a useful treatment option for FMF patients prior to initiating biological agents, particularly for those experiencing side effects or an inadequate response to coated colchicine (7,9). In line with this data, according to Türkiye's reimbursement rules, FMF patients are initially treated with coated colchicine. If they exhibit resistance or intolerant to this form, they are then prescribed compressed colchicine. For patients whose disease remains uncontrolled (characterized by persistent inflammation or frequent attacks) after six months of compressed colchicine therapy, IL-1 inhibitors, such as anakinra and canakinumab, are added to the treatment regimen. However, despite the expanded treatment options in FMF, subclinical or chronic inflammation can be seen in 15-25% of FMF patients (10). These treatment steps can be considered as an indicator of disease severity.

All chronic inflammatory rheumatic diseases (CIRDs) are associated with an increased risk of comorbidities, such as cardiovascular diseases, malignancies, infections, gastrointestinal diseases, osteoporosis, and depression (11,12). However, data on FMF and comorbidities in the literature are limited. Comorbidities in FMF are mainly studied in pediatric patients and are categorized into three groups: inflammation-related, FMF associated, and incidental (13). In a study, 158 adult FMF patients were evaluated, and the frequency of non-FMF-associated comorbidities was 21% and the most common comorbidity was hypertension (14).

Although research on FMF related conditions exists, there is a notable lack of studies focusing on comorbidities, particularly among adult FMF patients. Additionally, no studies have explored the relationship between FMF disease severity, treatment strategies, and the presence of comorbidities. Evaluating this situation is particularly important in our country, where FMF is prevalent, and colchicine preparations with different pharmacokinetic properties are used before IL-1 inhibition. As in other CIRDs, awareness of comorbidities in FMF plays an important role in disease management. Since FMF is a disease with a long course, awareness of the accompanying comorbidities will contribute to the patient general well being. This study aimed to address this gap by assessing comorbidities in FMF patients and examining whether severe disease is associated with these comorbidities.

Material and Method

The FMF patients who were followed at Ankara Bilkent City Hospital evaluated retrospectively between May 2019 and March 2024. Patients diagnosed with FMF by a rheumatologist were included in the study. Patients under 18 years of age and patients with any other rheumatological disease accompanying FMF were excluded from the study. Demographic variables, family history of FMF, FMF treatments, and comorbidities of patients were evaluated. The screened comorbidities from records were hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, arrhythmia, chronic kidney disease (CKD), non-renal amyloidosis, chronic obstructive pulmonary disease, asthma, thyroid disease, depression,

demyelinating diseases, neuropathy (non-diabetic), cerebrovascular disease, osteoporosis, and history of malignancy. The accompanying comorbidities were obtained from the medical records of the patients. We grouped patients based on their treatments. Because Türkiye's reimbursement guidelines allow different treatment options according to disease severity in patients with FMF. In Türkiye, coated colchicine is the first-line treatment for FMF, while compressed colchicine (sourced from abroad) is used for patients who are resistant to the coated form. According to the national healthcare reimbursement rules, both forms of colchicine must be attempted before progressing to IL-1 inhibitors. Thus, FMF treatments were categorized into three groups: coated colchicine, compressed colchicine, and IL-1 inhibition. Patients initially receiving coated colchicine were transitioned to compressed colchicine if they exhibited colchicine resistance or intolerance. Colchicine resistance was defined as experiencing at least one attack per month despite taking the maximum tolerated dose of colchicine for a minimum of three months, along with elevated levels of C-reactive protein and serum amyloid A between attacks. If resistance or intolerance continued with compressed colchicine, IL-1 inhibitors were added in for these patients. Additionally, if amyloidosis was detected at any stage, IL-1 inhibition was introduced alongside colchicine treatment.

The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Ankara Bilkent City Hospital No 1 approved the study protocol (Date:06/09/2023, Ethical approval number: E1-23-3897). Statistical analyses were conducted using Jamovi v2.3.22 (Sydney, Australia). Both visual methods (such as histograms and probability plots) and analytical methods (like the Kolmogorov-Smirnov test) were employed to assess the normality of the variables. Continuous variables that followed a normal distribution were presented as mean ± standard deviation (SD). Categorical variables were expressed as numbers and percentages. Comparisons between groups were performed using ANOVA for continuous variables and the chi-square test for categorical variables. Further pairwise comparisons were conducted using the Bonferroni method to adjust for multiple testing and minimize the risk of Type I error.

Results

The study included 740 FMF patients. The mean age (SD) of FMF patients was 40.7 (13.3), and 62.4% were female. Among all FMF patients, 75.4% were receiving coated colchicine, 13.3% were receiving IL-1 inhibitors with colchicine, and 11.3% were receiving compressed colchicine. The initial coated colchicine treatment was changed in a total of 24.5% to compressed colchicine, a further step up was done in 13.2% to IL-1 inhibition. 44.7% of all patients had at least one comorbidity. The three most common comorbidities were hypertension (20%), hyperlipidemia (7%) and depression (6.9%).

Table I. Demographic characteristics and comorbidities of the FMF patients

	Coated colchicine, n=588	Compressed colchicine, n=84	IL-1 inhibitor, n=98	All patients	*p value*
Age, year, mean (SD)	41.5 (13.6)	38.1 (12.1)	38.2 (11.9)	40.7 (13.3)	*0.020*
Female, n (%)	355 (60)	54 (64)	53 (54)	462 (60)	*0.350*
Family history of FMF, n (%)	73 (13)	19 (23)	12 (12)	104 (14)	*0.035*
Any comorbidity, n (%)	238 (41)	37 (32)	56 (57)	321 (42)	*0.002*
Hypertension, n (%)	111 (19)	10 (12)	28 (29)	149 (19)	*0.015*
Diabetes mellitus, n (%)	36 (6)	4 (5)	5 (5)	45 (6)	*0.900*
Hyperlipidemia, n (%)	39 (7)	6 (7)	7 (7)	52 (7)	*0.970*
Coronary artery disease, n (%)	11 (2)	2 (2)	1 (1)	14 (2)	*0.800*
Arrhythmia, n (%)	9 (2)	1 (1)	0	10 (1)	*0.640*
Chronic kidney disease, n (%)	13 (2)	0	20 (20)	33 (4)	*<0.001*
Non-renal amyloidosis, n (%)	2 (0.3)	0	1 (1)	3 (0.4)	*0.560*
Chronic obstructive pulmonary disease, n (%)	7 (1)	3 (4)	1 (1)	11 (1)	*0.170*
Asthma, n (%)	33 (6)	3 (4)	3 (3)	39 (5)	*0.580*
Thyroid disease, n (%)	29 (5)	4 (5)	1 (1)	37 (5)	*>0.999*
Depression, n (%)	44 (8)	4 (5)	3 (3)	51 (7)	*0.200*
Demyelinating diseases, n (%)	3 (1)	1 (1)	0	4 (0.5)	*0.430*
Neuropathy (non-diabetes mellitus), n (%)	4 (1)	0	0	4 (0.5)	*>0.999*
Cerebrovascular disease, n (%)	3 (1)	0	3 (3)	6 (1)	*0.060*
Osteoporosis, n (%)	13 (2)	1 (1)	1 (1)	15 (2)	*0.900*
Malignancy, n (%)	3 (0.5)	1 (1)	2 (2)	6 (1)	*0.150*

FMF: Familial Mediterranean fever, IL-1: Interleukin-1, SD: Standard deviation

Demographic characteristics and comorbidities of FMF patients according to treatment groups was shown in Table I. The mean age of patients in the coated colchicine group was higher than in patients receiving both compressed colchicine and IL-1 inhibition. Gender distribution was similar between groups (*p=0.350*). The frequency of patients with a family history of FMF was higher in the compressed colchicine group than in the coated colchicine and IL-1 inhibitor groups (23% vs. 13% and 12%, *p=0.035*, respectively). Comparison of FMF patients comorbidities according to treatment groups; at least one comorbidity was observed in 57% of IL-1 inhibitor group, 41% coated colchicine group, and 32% compressed colchicine group. The frequency of hypertension and chronic kidney disease was higher in the IL-1 inhibitor group than in the coated colchicine and compressed colchicine groups (29% vs. 19% and 12%, *p=0.015*, and 20% vs. 2% and 0%, *p<0.001*, respectively). In the subgroup analysis, any comorbidity was significantly more prevalent in the IL-1 inhibitor group (n=56/98, 57%) compared to the compressed colchicine group (n=27/84, 32%; *p<0.001*) and the coated colchicine group (n=238/588, 41%; *p=0.004*). Hypertension was found to be more common in the IL-1 inhibitor group (29%) compared to the compressed colchicine group (12%; *p=0.006*).

Chronic kidney disease was significantly more common in the IL-1 inhibitor group (n=20/100, 20%) compared to both the compressed colchicine group (0%; *p<0.001*) and the coated colchicine group (n=13/588, 2.2%; *p<0.001*). Family history was more common in the compressed colchicine group (n=19/84, 23%) compared to the coated colchicine group (n=73/588, 12%; *p=0.011*). Other variables, including age, gender, and other comorbidities, showed no statistically significant differences across the treatment groups.

Discussion

The key finding of our study was that almost half of the FMF patients, who were in their 40s on average, had a comorbidity. Our patients with FMF were largely treated with coated colchicine (75.4%), followed by IL-1 inhibitors (13.3%) and compressed colchicine (11.3%), as expected. Treatment adjustments were necessary for 24.5% of patients due to resistance or intolerability. We used treatment groups as a reflection of severe disease. The IL-1 inhibitor group displayed the highest comorbidity burden (57%), particularly with hypertension (29%) and chronic kidney disease (20%), compared to the coated and compressed colchicine groups. This trend suggests that these patients may have more complex clinical profiles, potentially due to organ damage. The findings emphasize the need for individualized screening strategies, particularly for patients with severe disease.

FMF is associated with subclinical or chronic inflammation, which can persist even between acute attacks. Persistent inflammation affects 15-25% of FMF patients, primarily due to active disease or comorbidities like spondyloarthritis and inflammatory bowel disease. Predictors include male gender, M694V homozygosity, colchicine resistance, and musculoskeletal attack dominance. Chronic inflammation is a significant risk factor for developing amyloidosis and other forms of organ damage (10). These findings highlight the importance of monitoring and managing chronic inflammation in FMF patients and carriers to prevent complications and improve outcomes. Colchicine is the primary treatment, but 5-15% of patients may not respond adequately despite optimal dosing (3,15,16). For colchicine-resistant or intolerant patients, IL-1 inhibitors showed substantial efficacy in reducing FMF flare frequency, managing inflammation, and improving patients' quality of life (17). Other treatment options for managing FMF include anti IL-6 agents, intra-articular glucocorticoids, nonsteroidal anti-inflammatory drugs, and disease-modifying anti-rheumatic drugs for chronic arthritis (18). In our study, initial colchicine therapy was adequate for 75% of patients, whereas 25% of patients needed a step up. Among these, 11.3% of the whole cohort could be controlled with compressed colchicine. However, 13.3% required IL-1 inhibitor therapy. We excluded FMF patients who had accompanying other rheumatological diseases.

In fact, all chronic inflammatory rheumatic diseases (CIRDs) are associated with an increased risk of comorbidities, including cardiovascular disease, infections, malignancies, gastrointestinal diseases, osteoporosis, and depression (19,20). These

comorbidities also contribute to higher healthcare costs, lower quality of life, and increased mortality rates in CIRD patients (12). Early detection and management of comorbidities should be an integral part of rheumatology patient care to improve overall health outcomes and reduce the risk of complications (21). When the coincidental comorbidities in FMF patients are analyzed, studies show that the frequency of osteoporosis is higher. In addition, anxiety and depression scores in quality-of-life assessments are more significantly affected (13,22). However, there are a limited number of studies in the literature addressing comorbidities in FMF patients. In a study by Tezcan et al. which evaluated non-FMF-associated comorbidities in 158 adult FMF patients, the comorbidities rate was found to be 21%, with hypertension as the most common one. The comorbidities assessed in this study included hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease (non-FMF related), chronic obstructive pulmonary diseases, and diabetes mellitus. In addition, in this study, the authors categorized FMF patients into two groups as mild and severe, based on the international severity scoring system for FMF criteria. Comorbidities were more prevalent in the severe FMF group compared to the mild group (39.1% vs. 18.5%, *p=0.02*) (14). Unlike Tezcan et al, half of all FMF patients in our study had at least one comorbidity. This discrepancy between the two studies may stem from the different FMF-related comorbidities evaluated. Nevertheless, similar to Tezcan et al.'s findings of an increased comorbidity rate among patients with high disease activity, our results also indicated a higher frequency of comorbidities among those receiving IL-1 inhibitor.

In our study, hypertension was the most common comorbidity, affecting 20% of all patients. Its prevalence was notably higher among patients receiving IL-1 inhibitor treatment, where it reached 29%. CKD was observed in 4% of all FMF patients. Additionally, the incidence of CKD alongside hypertension was significantly greater in the IL-1 inhibitor group compared to other groups. The risk of renal disease is known to increase in FMF patients. While amyloidosis related to the disease can affect multiple organs, the risk of renal amyloidosis is particularly elevated, often leading to proteinuria and CKD (23). CKD is thought to be strongly associated with renal amyloidosis. However, as our study relied on medication records rather than file reviews, and because the presence of renal biopsy in CKD patients could not be confirmed, we are unable to present conclusive data regarding amyloidosis. The rate of patients diagnosed with CKD in our study aligns with the reported prevalence of amyloidosis in the literature, which ranges from 2% to 10% (13,24). Chronic inflammation contributes to hypertension pathophysiology, with innate and adaptive immunity raising blood pressure through vascular inflammation and microvascular remodeling (25). The inflammation-hypertension relationship is bidirectional, with each condition potentially worsening the other (26). In patients at risk for renal disease, evaluating and managing coexisting hypertension may improve renal and cardiovascular health. On the other hand, hypertension is known to be one of the risk factors of CKD. High blood pressure increases the risk of development and progression of CKD (27). Hypertension and CKD are more common in patients on IL-1 treatment, likely due to resistant FMF and chronic inflammation. The fact that patients with any comorbidity were more common in the IL-1 inhibitor group may be related to the higher rates of hypertension and CKD in this group. Thus, managing both conditions is crucial for comprehensive FMF care.

Hyperlipidemia is the second most common comorbidity with 7% among all FMF patients. Chronic inflammation is a critical factor in the development of atherosclerosis and cardiovascular diseases, with hyperlipidemia being closely associated with inflammatory status (28). The relationship between inflammation and dyslipidemia is also bidirectional, lipids can activate inflammatory pathways, while cytokines can disrupt lipid metabolism (29). This interaction can create a vicious cycle of inflammation-dyslipidemia-inflammation, perpetuating both conditions (30). In our study, while hyperlipidemia was a notable comorbidity, there was no significant difference in its prevalence across the three patient groups, regardless of the treatment they were receiving. This suggests that other factors, potentially related to the underlying inflammatory process of FMF itself, may contribute more prominently to the

development of hyperlipidemia in these patients.

Depression was the third most common comorbidity among FMF patients in our study, with a prevalence of 6.9%. Inflammatory diseases, including FMF, are linked to higher rates of depression, as chronic inflammation and depression can mutually exacerbate each other (31,32). FMF patients often experience increased rates of depression, frequently accompanied by anxiety and sleep disturbances, which have been associated with higher disease activity (33,34). FMF also restricts daily activities, increases absenteeism and presenteeism, and negatively impacts work performance, which may contribute to mood disorders. Identifying and managing mood and sleep disorders are crucial for improving patient outcomes, as addressing these symptoms can enhance overall quality of life (35). While depression was more prevalent than comorbidities like hyperlipidemia, no significant difference was observed across the three treatment groups. Given the diagnostic challenges of depression, more targeted studies are needed to clarify potential differences between FMF treatment groups.

This study has several limitations. As it was retrospective and based on patient medication records, some data was incomplete. The frequency of comorbidities might differ from that observed in community-based screenings. Another limitation is that acute phase values or disease severity score scales could not be used when comparing treatment groups. While patients with known CKD were included, renal biopsy results were unavailable. Additionally, FMF-related comorbidities and MEFV genetic results could not be assessed due to data access issues, which limited analysis of genetic associations. The switch from coated to compressed colchicine due to intolerance may not indicate true colchicine resistance, meaning transitions in FMF treatment may not always reflect uncontrolled inflammation. Another limitation is the lack of duration data regarding medical treatments and comorbidities.

In conclusion, our retrospective analysis of FMF patients revealed that hypertension, hyperlipidemia, and depression are common comorbidities. While FMF is primarily an inflammatory rheumatologic disease marked by attacks, these comorbidities may be linked to underlying subclinical or chronic inflammation. Particularly in patients requiring IL-1 inhibitors, comprehensive evaluation of comorbidities is essential for better management of end-organ damage, reducing complications, and improving quality of life. It is crucial to assess FMF patients not only for the disease itself but also for accompanying symptoms and comorbidities, employing a multidisciplinary approach when needed.

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