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Infection frequency may not increase in Familial Mediterranean fever

Ailevi Akdeniz ateşinde enfeksiyon sıklığı artmayabilir

Nesrin Şen[1], Rıdvan Mercan[2], Ömür Volkan[1], Esra Bayar[3], Sibel Yılmaz-Öner[1], Mehmet Engin Tezcan[1]

[1]University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Rheumatology, İstanbul, Turkey
[2]Namık Kemal University Faculty of Medicine, Department of Rheumatology, Tekirdağ, Turkey
[3]Sivas State Hospital, Clinic of Internal Medicine, Sivas, Turkey

Abstract

Objective: To the best of our knowledge, there is no study evaluating the infectious features of Familial Mediterranean fever (FMF) in the literature. Here, we tested two hypotheses: infection is more common in FMF and FMF severity and infection may be linked.

Methods: We included three groups: FMF (363 patients), spondyloarthropathy (SpA-patients) (112 patients) and control (121 patients). We screened participants for infection characteristics in the last year with a pre-approved and validated questionnaire. Firstly, we compared infection rates, frequency of infection types, and infection severity within groups. We then evaluated the factors associated with infection in FMF.

Results: We found that infection rates were similar in FMF, SpA-patients and controls. However, admission to the infection outpatient clinic was more common in FMF (p=0.001) and the duration of workforce loss due to infection was longer in FMF than controls (p=0.002). Furthermore, FMF-patients with infection had higher disease severity (p=0.004), high acute phase reactants between attacks (p=0.006) and more site involvement during attacks (p<0.001). In multivariate analyses, the latter was found to be significant (p=0.003).

Conclusion: We discovered no increase in the infection rate of FMF patients. Patients with infections, on the other hand, may have more severe FMF.

Keywords: Auto-inflammatory diseases, disease activity, Familial Mediterranean fever, infection

Öz

Amaç: Literatürde Ailevi Akdeniz ateşi (AAA) enfeksiyon özelliklerini değerlendiren bir çalışma bulunmamaktadır. Bu çalışmada, iki hipotezi test ettik: enfeksiyon AAA'da daha yaygın olabilir ve AAA şiddeti ile enfeksiyon arasında bir ilişki olabilir.

Yöntem: Çalışmaya üç ayrı grup dahil ettik: AAA (363 hasta), spondiloartropati (SpA) (112 hasta) ve kontrol (121 hasta). Katılımcıları son bir yıl içindeki enfeksiyon özellikleri açısından önceden onaylanmış ve geçerli bir anketle taradık. İlk olarak, gruplar içinde enfeksiyon oranlarını, enfeksiyon türlerinin sıklığını ve enfeksiyonun şiddetini karşılaştırdık. Daha sonra AAA'da enfeksiyonla ilişkilendirilen faktörleri değerlendirdik.

Bulgular: AAA, SpA-hastaları ve kontroller arasında enfeksiyon oranlarının benzer olduğunu bulduk. Ancak, enfeksiyon polikliniğine başvuru AAA'da daha yaygındı (p=0,001) ve enfeksiyon nedeniyle iş gücü kaybının süresi AAA'da kontrollere göre daha uzundu (p=0,002). Ayrıca, enfeksiyonlu AAA hastalarının daha yüksek hastalık şiddeti (p=0,004), ataklar arası yüksek akut faz reaktanları (p=0,006) ve ataklar sırasında daha fazla bölge tutulumu (p<0,001) vardı. Çoklu değişken analizlerinde, sonuncusunun önemli olduğu bulundu (p=0,003).

Sonuç: Çalışmamızda AAA hastalarının enfeksiyon oranında artış gözlenmemiştir. Bununla birlikte, enfeksiyonlu hastaların daha şiddetli AAA'ya sahip olabileceği görülmüştür.

Anahtar Kelimeler: Oto-enflamatuvar hastalıklar, hastalık aktivitesi, Ailevi Akdeniz ateşi, enfeksiyon

Introduction

Infection is a leading cause of morbidity and mortality in rheumatic diseases. Infections could be triggered by both the diseases themselves and the treatments for these auto-inflammatory and auto-immune diseases. Infections in Familial Mediterranean fever (FMF) can, however, cause serious illness.[1] The main factors that increase the risk of infection in systemic lupus erythematosus (SLE) are impaired cellular and humoral immune functions.[2] Furthermore, even before the use of biologic

Correspondence / İletişim:
Mehmet Engin Tezcan MD, University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Rheumatology, İstanbul, Turkey
Phone: +90 216 458 30 00 **E-mail:** engintez@yahoo.com **ORCID ID:** orcid.org/0000-0002-1753-4936
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disease-modifying rheumatologic drugs, the rate of infection in rheumatoid arthritis (RA) patients was higher than in the general population.[3] On the other hand, disease activities may be linked to increased infection frequency. In the RADIUS-1 cohort, RA patients were found to be at higher risk of infection correlating with increased disease activity.[4] Additionally, hospitalization for infection in SLE patients was linked to disease activity, regardless of corticosteroid dose.[5] However, majority of infection risk is attributed to treatment in rheumatological diseases. Regardless of disease, immunosuppressive therapies, including corticosteroids, alkylating agents, all conventional synthetic, biologic, and targeted synthetic disease-modifying drugs, pose serious infection risks.[6-8]

FMF is an auto-inflammatory disease characterized by recurrent episodes of fever and polyserositis.[9] The majority of the mutations associated with auto-inflammatory diseases are directly linked to the innate immune system.[10] Pyrin is an inflammasome sensor that is often activated in response to infective pathogens.[11] During an infection, it increases both local and systemic inflammation while decreasing bacterial load.[12] In FMF and cryopyrinopathies, pyrin and cryopyrin mutations, respectively, are the main changes associated with the auto-inflammatory clinical spectrum.[13] Pyrin mutations may limit the immune system's first line of defence against pathogens in the above setting. In addition, infectious insults can cause uncontrolled inflammation, which can lead to attacks. As far as we know, although pyrin is mutated in FMF, there is no study in the literature that evaluates the propensity for infection in patients with FMF. Also, recurrent infections in FMF patients are risk factors for the development of amyloidosis and can cause progression as seen in amyloid storm during amyloidosis.[14] Infection, which is one of the environmental factors, can also influence the disease progression.[1]

In this study, we tested the validity of our two hypotheses. Our first hypothesis is that FMF patients, like other rheumatic diseases, have a higher risk of infection than the general population due to mutation in pyrin. Our second hypothesises that severe FMF and infection are linked.

Material and Methods

Study Participants' Characteristics and Selection Methods

The study group included 363 FMF patients who met the Tel-Hashomer Criteria.[15] The study included all consecutive FMF patients who presented within a one-year period and met the inclusion criteria. All FMF patients who had taken conventional synthetic, biologic, and targeted disease-modifying drugs, corticosteroids, and immunosuppressive drugs including interleukin (IL)-1 blockers for at least 18 months were excluded from the study. Here, thirty patients were excluded because they were taking an IL-1 blocker, and four were excluded because they were taking other anti-inflammatory disease-modifying drugs, corticosteroids, or immunosuppressive drugs. Additionally, we included two different control groups. The first included 112 spondylarthritis (SpA) patients who met the classification criteria of Assessment of Spondylarthritis International Society for SpA as the diseased control.[16] The study included all consecutive SpA patients who presented to the rheumatology outpatient clinic within three months and had not used conventional synthetic, biological, or targeted disease-modifying drugs, corticosteroids, or immunosuppressive drugs for at least 18 months. This was our disease control group. One of the reasons for including this group was to assess our performance on the task and the test's validity. The other group consisted of healthy controls who were matched with FMF patients in a 3:1 ratio for age (mean age ± standard deviation) and gender. Healthy controls were selected among those who applied to occupational health outpatient clinics for routine care. The healthy control group excluded people who had known inflammatory diseases or were taking immunosuppressive drugs. Participants in the three groups were excluded form study if they were under the age of 18 or over the age of 65, those with malignancy, pregnancy, had a diagnosis of primary or secondary immunodeficiency, or were breastfeeding. All participants were literate and perceptive. In total, 596 patients were participated in the trial, which was separated into three distinct groups.

Research Variables and Methods

We used a pre-approved and validated questionnaire to screen all participants' infectious disease characteristics, outcomes, and overall infection risk factor in the previous 12 months.[17] We used this questionnaire to assess the frequency and types of infection by asking, "How often have you had specific infections in the last 12 months?" [upper respiratory tract infections (URTI); urinary tract infection (UTI); gastro-intestinal tract infection, invasive mucosal infections, pneumonia, mucosal herpes infections and other unclassified infections], the frequency of antibiotic prescription by asking "How often did a physician prescribe antibiotics (drugs against infections; but no ointments for external use) in the past 12 months?", the characteristics of vaccination by questioning" Have you ever been vaccinated against specific disease?" (fully vaccination for pneumococcus and vaccinated for influenza in the past year), the need for hospitalization for infectious diseases by inquiring "How

often did you receive inpatient care in the past 12 months due to an infectious disease?" (stay in hospital wards at least overnight for infection diagnosis or treatment), frequency and number of applications to infectious diseases outpatient clinics by asking "How often did you receive outpatient care (medical practice or clinic) in the past 12 months due to an infectious disease?" (not hospitalized overnight, but a visits clinic for infection diagnosis or treatment) and the number of days lost in workforce due to infection in the past 12 months by asking "How many working days were you on sick leave in the past 12 months due to an infectious disease?" In addition, the risk factors for infectious diseases in the past 12 months such as hospitalization for non-infectious diseases and length of stay, surgery in the past year, removal surgeries for lymphoid tissues (appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision) at any time and organ/systemic specific infections at any time (sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection) were evaluated.

Demographic characteristics including age, gender, smoking history, and comorbidities (hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus) were collected from all study participants. Additionally, in both FMF and SpA groups, disease duration and disease activity were recorded. Here, the International Severity Scoring System for FMF (ISSF) was used to evaluate the severity of the disease which ranges from 0 to 10, where 10 is the most severe.[18] Furthermore, patients were classified as severe disease (≥6), intermediate disease (3-5) and mild disease (≤2) based upon ISSF scores. Also, ASAS-endorsed disease activity score (ASDAS) was used to assess the disease activity of patients with SpA.[19]

We obtained additional information from the FMF patients. Age of onset of symptoms, FMF related symptoms, MEFV mutations, if available, frequency, severity and duration of attacks, acute phase reactant levels over the previous year, presence of amyloidosis and FMF treatment were all recorded.

We also collected information from patients who had been infected with Coronavirus disease-2019 (COVID-19) infection. However, our hypothesis did not include assessing the outcome or severity of COVID-19 in FMF patients. We assigned COVID-19 to infection types in terms of disease involvement. We also highlight the COVID-19 data separately.

First, we compared the three groups in terms of the infectious disease frequency, infection types, and outcomes. Then, for only FMF-related parameters and infection risk factors, we compare FMF patients with and without infection. Finally, we looked at the relationship between disease severity and infectious disease features in FMF patients. We divided disease severity into two categories: Mild disease (ISSF ≤2) and moderate-severe disease (ISSF ≥3).

This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration (date: 09.03.2022, approval number: 2022/514/221/4 - University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee). All the patients gave written informed consent.

Statistical Analyses

Statistical analyses were carried out using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). To determine if the data were normally distributed, the Kolmogorov-Smirnov test was performed. None of the parameters distributed normally. Therefore, firstly, comparisons of continuous variables were made by Kruskal-Wallis or Mann-Whitney U according to the number of groups. In addition, chi-square test was used to compare categorical variables. We then performed post-hoc analysis with Bonferonni adjusted Mann-Whitney U or chi-square tests if necessary. We also performed multivariate analyses with logistic regression analyses to assess FMF related parameters and infection risk factors associated with infection in FMF patients. We included age, gender, colchicine dose (mg/day) and significantly different variables found in univariate analyses except individual attack sites into the model. We think that number of different attack sites represents all these variables. We calculated the sample size of the study with G*Power (Universität Kiel, Germany). At 95% power, α error level 0.05, and effect size 0.5, the total number of participants needed was 280 (210 cases/70 controls). P-value lower than 0.05 was considered as statistically significant. The categorial parameters were presented as numbers and percentages consecutively and continuous variables were shown as median (interquartile range). Infection frequencies, number of outpatient visits, length of stay and number of days lost in work were calculated in only positive cases.

Results

Demographic Characteristics of the Participants

The prevalence of male patients in the SpA group was observed to be higher compared to both FMF patients

and the control group (p=0.01). Furthermore, the median age in the SpA group was the highest among the studied groups, and SpA patients were significantly older than those with FMF (p<0.001). Notably, comorbidities were more frequently identified in SpA patients in comparison to the other groups (p<0.001).

It is noteworthy that none of the patients in the SpA cohort exhibited reactive arthritis. Among the 363 FMF patients, nine (4.1%) were diagnosed with amyloidosis. Importantly, none of these amyloidosis patients required dialysis, and none had a glomerular filtration rate below 30 mL/min. Conversely, none of the SpA patients were found to have amyloidosis in this study.

Infection Characteristics of Study Groups

Our first hypothesis is that FMF patients, like other rheumatologic disorders, have an elevated infection risk.

While the infection frequency in the previous year was statistically similar in all three groups, both the FMF group and the control group experienced a higher total number of infection attacks compared to patients with SpA in the last year (p=0.001). Furthermore, the number of different types of infections in FMF patients and the control group was higher than in SpA patients (p=0.001).

The frequency of specific infection types in FMF patients and the control group was generally similar, except for URTI, which were significantly higher in the control group (p=0.003). Although SpA patients had a higher frequency of comorbidities than the other groups, the frequency of infection types was either similar or lower than the other two groups. URTI and UTI were identified as the most common types of infections in FMF patients.

Notably, the prevalence of COVID-19 in the past year was similar across all groups. Only one patient in each group experienced COVID-19-related pneumonia, while the remaining cases were characterized by upper respiratory tract infections. The only risk factor for infections that differed significantly between FMF patients, and the control group was surgical removal of lymphoid tissues at any time (p=0.04). In this study, FMF patients had a higher rate of appendectomy than the control group. Vaccination characteristics were similar between the FMF and control groups. In addition, none of the study participants had been admitted to the intensive care unit in the previous year for infectious or non-infectious conditions.

In individuals with FMF, there was a notable increase in both the frequency of visits to the infectious disease outpatient clinic (p=0.002) and the duration of work absenteeism due to infection (p=0.003) when compared to the control group. Conversely, in patients with SpA, these factors were found to be comparable to those in the control group.

Demographic and infection disease characteristic of the participants were shown in Table 1.

FMF Characteristics of Patients with or without Infection in the Past Year

Our second hypothesis is that FMF severity is related to infection. First, we assessed disease features such as disease severity as a risk factor for infection.

Demographic characteristics were similar between the patients with or without infection in the past year.

Pleuritis, fever, arthritis, exertional leg pain and myalgia were more common in FMF patients who had an infection in the last year. However, none of the FMF patients in our cohort met the International Society for Spondylarthritis Assessment of Spondylarthritis classification criteria. Furthermore, the infected FMF group had higher ISSF scores, a higher frequency of increased acute phase reactants between attacks, and a higher number of different sites involved in FMF episodes.

The infected group received influenza vaccine at a higher rate than the uninfected group (p=0.03). Furthermore, the frequency of hospitalization for non-infectious conditions was higher in the infected group (p=0.01). All other infection risk factors were similar between groups.

Disease and infection characteristics of infected and non-infected FMF patients in the past year was shown in Table 2.

In multivariate analyses, the only variable associated with infection in FMF patients was number of different sites involved during attack (odds ratio: 1.48, 95% confidence interval: 1.12-1.75, p=0.003) (Table 3).

Demographic and Infectious Characteristics of FMF Patient Classified in Terms of Disease Severity

As part of our second hypothesis, we examined the infectious characteristics of FMF patients with severe disease to determine the significance of disease severity in infection.

Patients with FMF who had moderate-to-severe disease were prescribed a higher median colchicine dose compared to those with mild disease (p=0.005). In the previous year, both groups showed similar frequencies and total numbers of infection attacks. However, there was a tendency towards an increased infection frequency in the last year among patients with moderate-to-severe FMF compared to those with mild disease. Additionally, individuals with more severe disease experienced a higher frequency of both URTI (p=0.008) and COVID-19 (p=0.03).

Table 1. Demographic and infection disease characteristic of the participants

	FMF n=363	SpA n=112	Control n=121	p	Post-hoc analyses
Gender (M/F)	123/240*	55/57*+	41/80+	0.01	0.004*
					0.001+
Age (years)	33.0 (25.0-43.0)*	38.0 (31.0-46.7)*	34.0 (24.0-42.0)	<0.001	<0.001*
Disease duration (years)	8.0 (4.0-14.0)	6.0 (3.0-12.0)	N/A	0.03	
Smoking, n (%)	94 (25.9)	38 (33.9)	38 (31.4)	0.16	
Comorbidity, n (%)[1]	57 (15.7)*^	29 (25.9)*+	7 (5.8)^+	<0.001	0.01*^
					<0.001+
ISSF score	1.0 (1.0-3.0)	N/A	N/A		
ASDAS	N/A	2.5 (2.5-2.5)	N/A		
Infection characteristics[2]					
Infection in the past year, n (%)	241 (66.4)	61 (54.5)	75 (62.0)	0.06	
Total number of infections in the past year (n)	2.0 (1.0-3.0)*	1.0 (1.0-2.0) *+	2.0 (1.0-3.0) +	0.001	<0.001*+
URTI, n (%)	143 (39.4)^	43 (38.4) +	68 (56.2) ^+	0.003	0.001^
					0.007+
Frequency of URTI (n)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.43	
Pneumonia, n (%)	18 (5.0)	5 (4.5)	9 (7.4)	0.51	
Frequency of pneumonia (n/year)	1.0 (1.0-1.0)	1.0 (1.0-1.5)	1.0 (1.0-1.0)	0.89	
UTI, n (%)	113 (31.1)*	16 (14.3)*	28 (23.1)	0.009	<0.001*
Frequency of UTI (n/year)	1.0 (1.0-2.0)^	1.0 (1.0-1.0)	1.0 (1.0-1.0)^	0.009	0.004^
GTI, n (%)	47 (12.9)*	3 (2.7)*+	16 (13.2) +	0.007	0.002*
					0.003+
Frequency of GTI (n/year)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.43	
Invasive mucosal infections, n (%)	20 (5.5)	1 (0.9)	6 (5.0)	0.77	
Frequency of invasive mucosal infections (n/year)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (1.0-2.5)	0.77	
Mucosal herpes infection, n (%)	46 (12.7)*	2 (1.8)*+	11 (9.1)+	0.003	0.001*
					+0.01+
Frequency of herpes infection (n/year)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.21	
Other infections, n (%)	15 (4.2)	7 (6.3)	1 (0.8)	0.28	
COVID-19*, n (%)	20 (5.5)	8 (7.1)	2 (1.7)	0.12	
Number of different types of infection (n)	2.0 (1.0-2.0)*	1.0 (1.0-2.0)*+	2.0 (1.0-3.0)+	0.001	0.004*
					<0.001+
Prescript antibiotics in the past year, n (%)	187 (51.5)	47 (42.0)	50 (41.3)	0.09	
1-3 times	152 (41.9)	43 (38.4)	46 (38.0)		
4-6 times	25 (6.9)	3 (2.7)	3 (2.5)		
>6 times	10 (2.8)	1 (0.9)	1 (0.8)		
Application to infection disease outpatient clinic, n (%)	105 (28.9)^	31 (27.7)+	16 (13.2)^+	0.002	0.001^
					0.006+
Number of applications to infection disease outpatient clinic (n)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	0.07	
Hospitalization due to infection in the past year, n (%)	19 (5.2)	2 (1.8)	0 (0)	0.12	
Duration of hospitalization due to infection (day)	2.0 (1.0-5.0)	1.0 (1.0-1.0)	N/A	0.19	
Loss of workforce due to infection in the past year, n (%)	45 (12.4)	9 (8.0)	7 (5.8)	0.08	
Loss of workforce due to infection (days)	10.0 (5.0-12.0)^	10.0 (7.5-20.0)+	4.0 (2.0-5.0)^+	0.003	0.002^
					0.001+
Infection risk factors/precautions					
Surgery in the past year, n (%)	16 (4.4)	2 (1.8)	0 (0.0)	0.20	
Hospitalization due to noninfection diseases in the past year, n (%)	16 (4.4)	8 (7.1)	1 (0.8)	0.05	
Removal surgeries of lymphoid tissues at any time, n (%)[3]	60 (16.5)^	9 (8.0)	8 (6.6)^	0.04	0.007^

Table 1. Continued

	FMF n=363	SpA n=112	Control n=121	p	Post-hoc analyses
Pet ownership, n (%)	22 (6.1)	12 (10.7)	5 (4.1)	0.10	
Full vaccinated for pneumococcus, n (%)	8 (2.2)	5 (4.5)	3 (2.5)	0.42	
Vaccinated for influenza in the past year, n (%)	18 (5.0)	2 (1.8)$^{+}$	13 (10.7)$^{+}$	0.009	0.005^{+}
Organ/system specific infections at any time, n (%)[4]	2 (0.9)	2 (1.8)	1 (0.8)	0.45	

ASDAS: ASAS-endorsed disease activity score, COVID-19: Coronavirus disease-19, F: Female, GTI: Gastro-intestinal tract infection, ICU: Intensive care unit, ISSF: The International Severity Scoring System for FMF, M: Male, URI: Urinary tract infection, URTI: Upper respiratory tract infections

[1]Comorbidities: Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.

[2]Infection frequencies, number of outpatient visits, length of stay and number of days lost in work were calculated in only positive cases.

[3]Organ/system specific infections: Sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection,

[4]Removal surgeries: Appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision.

**: The difference between FMF and SpA patients in post-hoc analyses*

+: The difference between SpA patients and controls in post-hoc analyses

^: The difference between FMF patients and controls in post-hoc analyses

COVID-19 patients were also classified according to the type of involvement. P<0.05 was significant. P<0.016 was significant in post-hoc analyses

Moreover, patients with moderate-to-severe FMF exhibited a higher frequency of admissions to the infectious disease outpatient clinic (p=0.03) and experienced greater work loss due to infection (p=0.04) than those with mild FMF.

It is noteworthy that all infection risk factors and precautions were similar between the two groups. Demographic and infectious characteristics of FMF patient classified in terms of disease severity was shown in Table 4.

Discussion

In the study evaluating the validity of our two hypotheses about the relationship between FMF and infection, we found that FMF patients had same infection frequency as healthy controls and disease controls. However, FMF patients had a higher rate of admission to an infectious outpatient clinic and a longer duration of workforce loss in the previous year than the control group. Furthermore, even though the only independent factor related to infection in FMF patients was the number of locations involved during the attack, FMF patients who had infection in the previous year had more severe disease than patients who did not have infection. As a result, our initial hypothesis that FMF, like other rheumatic diseases, raises the risk of infection is not fully supported. However, the severity of FMF was higher in patients infected in the previous year, and these patients can be considered to have more severe infections based on the hospitalization frequency and loss of workforce due to infection.

To our knowledge, this is the first study to assess the infectious characteristics of FMF patients. The most common types of infections in our FMF patients were URTI and UTI. Bacterial etiologies are the most common cause of infection in SLE, followed by viral and fungal infections. The most common types of infection in SLE are respiratory tract, urinary tract, and skin infections.[2] In addition, the most common sites of infection in SpA patients were the respiratory tract, followed by the skin, genitourinary system, upper respiratory tract, sinuses, and gastrointestinal tract.[20] Furthermore, respiratory tract infections are the most common in RA patients, followed by skin and genitourinary system infections.[21]

In our study, the most common sites of infection in FMF patients were similar to other inflammatory diseases, such as the respiratory tract and genitourinary system. Infections in rheumatological conditions may be caused by defects in both the adaptive and innate immune systems.[22] In the innate immune system, neutrophil dysfunction, and deficiencies in their numbers due to pathological immune complex or antibodies can impair the first line of defense against pathogens.[23] Similarly, in many rheumatological diseases, adaptive immune system disorders caused by partial T-cell dysfunction may increase the frequency of infection.[24] As we mentioned before, the relationship between infection and disease severity can be bidirectional. Infection can cause severe attacks and amyloidosis, or severe disease can cause infection. According to our findings, infection could be a contributing factor to more severe FMF while triggering attacks. Several infectious pathogens have previously been linked to the onset of juvenile idiopathic arthritis.[25] As a result, while our study cannot establish a causal relationship, future prospective studies may investigate the role of infections in severe FMF. Although infection rates in all FMF patients, regardless of activity, are comparable to control groups, we believe that the uncontrolled, unprovoked, and increased inflammatory environment and dysfunction of pyrin protein in FMF may limit the resistance to pathogens in the mucosal regions such as respiratory and genitourinary tracts or frequent infections in common mucosal sites can cause severe disease.

Table 2. Disease and infection characteristics of infected and non-infected FMF patients in the past year

	FMF patients with infection n=241	FMF patients without infection n=122	p
Gender (M/F)	77/164	46/76	0.27
Age (years)	34.0 (25.0-43.0)	31.0 (25.0-43.0)	0.63
Age at FMF onset (years)	14.0 (8.0-20.0)	15.0 (8.0-23.2)	0.24
Disease duration (years)	8.0 (3.5-14.0)	8.0 (5.0-12.2)	0.93
Smoking, n (%)	65 (27.0)	29 (23.8)	0.51
Comorbidity, n (%)[1]	34 (14.1)	23 (18.9)	0.24
FMF disease characteristics			
Peritonitis, n (%)	217 (90.0)	112 (91.8)	0.66
Pleuritis, n (%)	112 (46.5)	36 (29.5)	0.002
Fever, n (%)	163 (67.6)	57 (46.7)	<0.001
Arthritis, n (%)	90 (37.3)	29 (23.8)	0.008
Erysipeloid erythema n (%)	38 (15.8)	22 (18.0)	0.60
Exertional leg pain, n (%)	66 (27.4)	22 (18.0)	0.04
Myalgia, n (%)	95 (39.4)	28 (23.0)	0.001
Enthesitis, n (%)	21 (8.7)	4 (3.3)	0.05
Amyloidosis, n (%)	8 (3.3)	1 (0.8)	0.15
Attacks per year	2.0 (1.0-6.0)	2.0 (0.0-6.0)	0.08
Attack duration (day)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.09
VAS attack score (0-100)	50.0 (30.0-70.0)	50.0 (30.0-70.0)	0.24
Number of sites involved during attack	3.0 (2.0-3.0)	2.0 (1.0-3.0)	<0.001
Colchicine dosage (mg/day)	1.0 (1.0-1.5)	1.0 (1.0-1.5)	0.19
Elevated acute phase reactants, n (%)[2]	101 (41.9)	33 (27.0)	0.006
MEFV exon 10 homozygotes, n (%)	33 (13.7)	12 (9.8)	0.82
ISSF score (0-10)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.004
Infection risk factors/precautions			
Surgery in the past year, n (%)	14 (5.8)	2 (1.6)	0.06
Hospitalization due to non-infection diseases in the past year, n (%)	15 (6.2)	1 (0.8)	0.01
Removal surgeries for lymphoid tissues at any time, n (%)[3]	41 (17.0)	19 (15.6)	0.72
Pet ownership, n (%)	17 (7.1)	5 (4.1)	0.26
Full vaccinated for pneumococcus, n (%)	7 (2.9)	1 (0.8)	0.20
Vaccinated for influenza in the past year, n (%)	16 (6.6)	2 (1.6)	0.03
Organ/system specific infections at any time, n (%)[4]	2 (0.8)	0 (0.0)	N/A

F: Female, FMF: Familial Mediterranean fever, ICU: Intensive care unit, ISSF: The International Severity Scoring System, M: Male, MEFV: Mediterranean fever gene, VAS: Visual analogue score.

[1]Comorbidities: Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.

[2]Erythrocyte sedimentation rate and/or C-reactive protein during attack free period at least two times 1 month apart (at least ≥ 2 weeks after the last attack)

[3]Organ/system specific infections: Sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection.

[4]Removal surgeries: Appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision. COVID-19 patients were also classified according to the type of involvement. p<0.05 was significant

Table 3. Multivariate analyses for risk factors for infections in FMF

	OR	95% CI	p
Male gender	1.41	0.86-2.29	0.16
Age	1.00	0.98-1.02	0.54
Number of sites involved during attack	1.48	1.12-1.75	0.003
ISSF score	1.07	0.88-1.29	0.47
Hospitalization due to non-infection diseases in the past year	0.17	0.02-1.38	0.09
Elevated acute phase reactants[1]	0.68	0.41-1.15	0.68
Colchicine dosage (mg/day)	1.16	0.69-1.95	0.56
Vaccinated for influenza in the past year	0.32	0.70-1.15	0.32

[1]Erythrocyte sedimentation rate and/or C-reactive protein during attack free period at least two times 1 month apart (at least ≥2 weeks after the last attack)

p<0.05 was shown bold, CI: Confidence interval, FMF: Familial Mediterranean fever, OR: Odds ratio, ISFF: The International Severity Scoring System

Table 4. Demographic and infection characteristics of FMF patient classified in terms of disease severity

	Mild disease n=257	Moderate-severe disease n=106	p
Gender (M/F)	87/170	36/70	0.98
Age (years)	33.0 (25.0-44.0)	32.5 (24.7-42.0)	0.23
Age at FMF onset (years)	15.0 (8.2-21.0)	11.0 (7.0-20.0)	0.002
Disease duration (years)	8.0 (4.0-14.0)	8.0 (4.0-13.0)	0.69
Smoking, n (%)	57 (22.2)	37 (34.9)	0.12
Comorbidity, n (%)[1]	42 (16.3)	15 (14.2)	0.60
Amyloidosis, n (%)	6 (2.3)	3 (2.8)	0.76
Colchicine dosage (mg/dL)	1.0 (1.0-1.5)	1.5 (1.0-1.5)	0.005
Infection characteristics[2]			
Infection in the past year, n (%)	163 (63.4)	78 (73.6)	0.06
Total number of infections in the past year (n)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.84
URTI, n (%)	90 (35.0)	53 (50.0)	0.008
Frequency of URTI (n)	1.0 (1.0-1.0)	1.0 (1.0-1.5)	0.79
Pneumonia, n (%)	13 (5.1)	5 (4.7)	0.89
Frequency of pneumonia (n/year)	1.0 (1.0-1.5)	1.0 (1.0-1.0)	0.50
UTI, n (%)	79 (30.7)	34 (32.1)	0.80
Frequency of UTI (n/year)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.86
GTI, n (%)	31 (12.1)	16 (15.1)	0.43
Frequency of GTI (n/year)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	0.26
Invasive mucosal infections, n (%)	17 (6.6)	3 (2.8)	0.15
Frequency of mucosal infections (n/year)	1.0 (1.0-2.5)	1.0 (1.0-2.0)	0.30
Mucosal herpes infection, n (%)	35 (13.6)	11 (10.4)	0.39
Frequency of herpes infection (n/year)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.61
Other infections, n (%)	12 (4.7)	3 (2.7)	0.15
COVID-19*, n (%)	10 (3.9)	10 (9.4)	0.03
Number of different types of infection (n)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.31
Prescript antibiotics, n (%)	128 (49.8)	59 (55.7)	0.79
Application to infection disease outpatient clinic, n (%)	66 (25.7)	39 (36.8)	0.03
Number of applications to infection disease outpatient clinic (n)	1.0 (1.0-2.0)	1.0 (1.0-3.0)	0.75
Hospitalization due to infection in the past year, n (%)	12 (4.7)	7 (6.6)	0.45
Duration of hospitalization due to infection (day)	3.0 (1.0-5.0)	1.0 (1.0-3.0)	0.29
Loss of workforce due to infection in the past year, n (%)	26 (10.1)	19 (17.9)	0.04
Loss of workforce due to infection (days)	10.0 (4.75-10.0)	10.0 (7.0-14.0)	0.38
Infection risk factors/precautions			
Surgery in the past year, n (%)	14 (5.4)	2 (1.9)	0.13
Hospitalization due to non-infection diseases in the past year, n (%)	9 (3.5)	7 (6.6)	0.19
Removal surgeries of lymphoid tissues at any time, n (%)[3]	39 (15.2)	21 (19.8)	0.28
Pet ownership, n (%)	16 (6.2)	6 (5.7)	0.83
Full vaccinated for *pneumococcus*, n (%)	4 (1.6)	4 (3.8)	0.19
Vaccinated for influenza in the past year, n (%)	11 (4.3)	7 (6.6)	0.35
Organ/system specific infections at any time, n (%)[4]	0 (0.0)	2 (1.9)	N/A

COVID-19: Coronavirus disease-19, M: Male, F: Female, FMF: Familial Mediterranean fever, GTI: Gastro-intestinal tract infection, ICU: Intensive care unit, ISSF: The International Severity Scoring System, MEFV: Mediterranean fever gene, URI: Urinary tract infection, URTI: Upper respiratory tract infections, VAS: Visual analogue score

[1]Comorbidities: Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.

[2]Infection frequencies, number of outpatient visits, length of stay and number of days lost in work were calculated in only positive cases.

[3]Organ/system specific infections: Sexually transmitted diseases, osteomyelitis, septic arthritis, endocarditis, infective nephritis, human immunodeficiency virus, zoster infection.

[4]Removal surgeries: Appendectomy, splenectomy, tonsillectomy, thymectomy, nasal polyp excision. COVID-19 patients were also classified according to the type of involvement.

p<0.05 was significant

There are several factors that may be associated with an increased risk of infection in rheumatic diseases.[21] In our study, the main risk factors for infection in FMF patients were disease severity, the number of sites involved during attacks, and elevated acute phase reactants between attacks. Therefore, we think that the severity of FMF and the parameters in the severity scale may be related to the increased risk of infection. Disease activity in RA and SLE is also associated with an increased risk of infection. All immunological dysfunctions associated with these diseases may increase during worse disease activity.[26,27] Likewise, the severity of FMF, which is characterized by high acute phase reactants during attack-free period, combined with widespread attacks may exacerbate the disorders in the immune system. Amyloidosis is more common in more severe FMF disease, particularly when acute phase reactants are high between attacks. Also, infection diseases may exacerbate accumulation of amyloid proteins in FMF patients with stable amyloidosis.[14] Thus, infections in these cases may play a dual role in the development and progression of amyloidosis.

In addition, patients with more severe FMF received a higher median colchicine dose. However, there is no definitive proof in the literature linking colchicine and infections.[28]

Some variables associated with severe infection, such as longer duration of loss of workforce due to infection and admission to the infectious outpatient clinic in the previous year, were found to be more common in FMF patients than in controls, but not in SpA patients. Furthermore, loss of workforce due to infection and admission to the infectious outpatient clinic in the previous year are more common in severe FMF cases than in mild cases. However, hospitalization due to infection, which is one of the serious infection indices,[29] did not change with the presence of FMF and the severity of the disease. However, based on the findings, we can speculate that infection and FMF severity may be linked, as in other rheumatological diseases.

We found that the infection frequency in the last year was similar in FMF patients to controls and SpA. We think that there are two reasons for this similarity. Although it may be controversial[30] receiving anti-tumor necrosis factor therapy is the main risk factor for infection in SpA. To rule out treatment effects, none of the SpA patients in our study had previously received immunosuppressive therapy. Therefore, infection rates in SpA were not higher than controls. Furthermore, SpA and FMF patients may have taken more COVID-19 prevention measures than controls.

Another noteworthy aspect is that episodes of FMF can present symptoms like infectious disease, potentially resulting in misdiagnosis and inappropriate treatment strategies. This underscores the importance of accurate differentiation between FMF and infectious conditions to ensure proper diagnoses and effective therapeutic approaches.

Study Limitations

There are some limitations to the study. To begin with, the information is based on the patent's response to a pre-approved questionnaire. The authors of the questionnaire urged researchers to use it with caution in the original paper. However, it has been demonstrated that it is quite reliable in detecting infection rates. Furthermore, they emphasized that the section on infectious risks should be improved. Finally, it is preferable to conduct a prospective study in which patients and medical databases are checked for infection on a weekly basis to avoid recall errors. Second, we did not confirm incidents of infection during the visits. and we only cross-sectionally looked at last year's infection data. Finally, the diseased control group of the study was SpA patients who were not on immunosuppressive drugs. This group has similar infection rate with general population. We did not include other rheumatological diseases, such as RA, because they cannot be studied without the use of immunosuppressive drugs. However, among rheumatological diseases, the SpA group has a lower infection rate, as expected. Despite the fact that, infectious diseases were clinically heterogeneous, we divided the patients based on having an infectious disease in the previous year and then compared the disease related features in infected and non-infected patients for the first time in the literature to show risk factors for any kind of infection in FMF patients. Finally, it's important to note that the questionnaire utilized in this study lacks validation in Turkish.

Conclusion

In summary, having FMF might not necessarily lead to a higher overall frequency of infections compared to individuals without the condition. However, individuals with severe FMF, as indicated by higher disease severity scores, may encounter more episodes of infectious attacks. Additionally, there appears to be a correlation where individuals who had an infection in the last year may also have increased disease severity.

Ethics

Ethics Committee Approval: This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration (date:

09.03.2022, approval number: 2022/514/221/4 - University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee).

Informed Consent: All the patients gave written informed consent.

Authorship Contributions

Concept: N.Ş., M.E.T., Design: M.E.T., Data Collection or Processing: R.M., Ö.V., E.B., S.Y.Ö., Analysis or Interpretation: N.Ş., M.E.T., Literature Search: R.M., S.Y.Ö., Writing: N.Ş., M.E.T.

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