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Original Article

COVID-19 in familial Mediterranean fever: Clinical course and complications related to primary disease

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ABSTRACT

Objectives: To evaluate the impact of familial Mediterranean fever (FMF) features on the clinical course and outcomes of coronavirus disease 2019 (COVID-19) and clinical course of FMF after COVID-19.

Methods: Consecutive FMF patients with COVID-19 were enrolled from three referral hospitals. Clinical features of FMF and detailed COVID-19 information were obtained from patient interviews and medical records.

Results: Seventy-three FMF patients were included in the study. 94.5% of patients had clinical symptoms of COVID-19. We found 24.7% hospitalization, 12.3% respiratory support, 4.1% intensive care unit admission, 6.8% complication, and 1.4% mortality rate in patients. The risk factors of hospitalization for respiratory support were male gender [OR: 7.167 (95% CI: 1.368–37.535)], greater age [OR: 1.067 (95% CI: 1.016–1.121)], and non-adherence to colchicine treatment before the infection [OR: 7.5 (95% CI: 1.348–41.722)]. One-third of patients had reported attacks after COVID-19. The patterns of triggered attacks were fever, peritonitis, pleuritis, transient arthritis, chronic knee mono-arthritis, and protracted febrile myalgia.

Conclusions: FMF characteristics were not associated with worse outcomes of COVID-19. Colchicine non-adherence was the risk factor of hospitalization for oxygen support. The rate of FMF attacks after COVID-19 is prominently increased, with some of them being protracted and destructive.

KEYWORDS: Coronovirus-19 disease; familial Mediterranean fever; clinical course; complication; outcome

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has affected every facet of life. Since the outbreak, a myriad of clinical studies have elucidated that COVID-19 is not considered as an ordinary viral infection in that it is a highly complex disease leading to severe lung inflammation, acute respiratory distress syndrome (ARDS), cardiac and renal injury, multiorgan failure, and thromboembolic events, especially in patients with older age and specific comorbidities [1–4]. Exaggerated systemic inflammation and dysregulated immune system, including the surge of pro-inflammatory cytokines, neutrophilia, blunted T-cell response, impaired type I interferon response, and overactivation of macrophages, have been observed in the course of the disease, which determines the disease severity and, eventually, the outcome [2, 5–9].

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder resulting from the gain of function mutations in the Mediterranean fever gene (*MEFV*) encoding inflammasome sensor protein, called pyrin, which plays a regulatory role in the innate immune system. *MEFV* gene mutations impair the regulation of pyrin inflammasome, causing uncontrolled activation of caspase-1, which induces the release of potent pro-inflammatory cytokines, interleukin (IL)-1 and IL-18, and activation of the gasdermin D pyroptotic pathway [10]. SARS-CoV-2 viral particles like E proteins directly trigger the nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome pathway resulting in cytokine storm and tissue injury [11, 12]. FMF is characterized by self-limiting attacks, and several factors might induce attacks, including infections [10]. Adverse fatal events have been reported after infections in FMF patients due to

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worsening of kidney functions and amyloid storm, which has not yet been investigated after COVID-19 [13].

Colchicine is the mainstay of FMF treatment, but 5–10% of patients do not respond well to treatment, especially those harbouring the M694V homozygous variant and severe disease phenotype. This agent has various effects on the innate immune system, including prevention of microtubule polymerization and generation, NLRP3 inflammasome activation responsible for IL-1β and IL-18 processing, suppression of chemotaxis, cellular adhesion molecules, and cytokines [10, 14]. Clinical trials assessing the efficacy of colchicine in patients with COVID-19 variously reported benefit, no effect or harm, probably due to different study designs and enrolled patient characteristics [15]. IL-1 antagonists, anakinra and canakinumab, are effective treatment choices in FMF patients with colchicine resistance or intolerance [10]. Moreover, anakinra is one of the recommended treatment options in patients with severe COVID-19 [16, 17].

In the view of noteworthy information, the relationship between FMF and COVID-19 has become an interest. Herein, we aimed to evaluate the clinical course and outcomes of COVID-19 in FMF patients and the effects of FMF characteristics on COVID-19 outcomes, such as hospitalization and respiratory support, and to assess flares of FMF attacks and FMF disease course after COVID-19.

Materials and methods

Study design and participants

Consecutive FMF patients who fulfilled Tel Hashomer criteria and confirmed COVID-19 by the SARS-CoV-2 nucleic acid real time-polymerase chain reaction (RT-PCR) test in nasopharyngeal swab/sputum or suggestive symptoms and computed tomography (CT) findings were enrolled in the study from three referral hospitals [18]. The study was approved by the Ministry of Health and Institutional Ethics Committee, and informed consents were obtained from the participants.

Data collection

Demographic data, clinical characteristics of FMF, detailed attack features, genetic mutation analysis, disease activity, comorbidities, used medications, and complications, like secondary amyloidosis and kidney failure, were obtained from patient interviews and electronic medical records. Colchicine resistance was defined as a presence of monthly attacks in 3 months in a row or consistently elevated acute phase reactants, whereas complete remission was defined as a complete absence of attacks and normal acute phase response within the 6-month period before the infection [19]. Detailed COVID-19 data, including symptoms, treatment modalities, complications such as ARDS, myocarditis, thromboembolism or bacterial infections, hospitalization, and outcomes, were recorded. The continuation of medications for FMF throughout the COVID-19 course and the effect of COVID-19 on FMF attacks after recovery were evaluated.

Statistical analysis

Statistical Package for the Social Sciences software v16.0 (SPSS Inc, Chicago, IL) and Microsoft Excel package programs were used for statistical analysis. The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests) to determine whether or not they are normally distributed. Descriptive analyses were presented using medians and in interquartile range terquartile range (IQR) for the non-normally distributed variables. The Mann–Whitney *U* test was used to compare these variables between the groups. Categorical data were described as absolute numbers and percentages. The chi-square test or Fisher's exact test was used to compare categorical variables. Regression analyses were performed to determine hospitalization risk factors for respiratory support during COVID-19. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CI). A p value of <.05 was considered statistically significant.

Table 1. Demographic characteristics of familial Mediterranean fever patients with COVID-19.

Age, years, median (IQR)	34 (16) (min-max:17–87)
Gender, female, *n* (%)	45 (61.6)
Smoking, *n* (%)	
Never	44 (60.3)
Ex-smoker	9 (12.3)
Active	20 (27.4)
Comorbidities, *n* (%)	33 (45.2)
Hypertension	9 (12.3)
Cardiovascular disease	2 (2.7)
Diabetes mellitus	3 (4)
Kidney failure	6 (8.2)
Chronic lung disease	2 (2.7)
Malignancy	1 (1.4)
Spondyloarthritis	12 (16.4)
Other comorbidities[a]	17 (23.3)
History of vaccination for COVID-19	2 (2.7)

[a]Other comorbidities include hypothyroidism, inflammatory bowel disease, psoriasis, kidney transplantation, chronic liver disease, fibromyalgia, juvenile chronic arthritis, and osteoporosis.

Results

Characteristic features of FMF patients

Seventy-three FMF patients were included in the study. The median age of patients was 34 years ranging from 17 to 87 years, and the median disease duration was 10 years. Almost half of the patients (45.2%) had at least one comorbidity, the most common of which were spondylarthritis (16.4%) and hypertension (12.3%) (Table 1). MEFV gene analyses were available for 59 patients, with 76% of patients having M694V mutation and 51% as homozygous genotype. All patients were on colchicine treatment and 23% of patients were receiving add-on IL-1 antagonist. With these treatments, 46 patients (64%) were in complete remission before the COVID-19 infection (Table 2).

The clinical course and outcomes of FMF patients with COVID-19

The COVID-19 diagnosis of sixty-six patients (90.4%) were confirmed by the SARS-CoV-2 RNA RT-PCR test. One-third of the patients had chest CT upon diagnosis, and three of them were unremarkable. Except for four patients, all patients (94.5%) had clinical symptoms of COVID-19; fever, upper respiratory tract symptoms, arthralgia-myalgia, and cough were the most frequent, respectively (Table 3). Sixty-six patients (90.4%) received COVID-19-specific treatment,

Table 2. Clinical features of FMF disease and current treatment in patients with COVID-19.

The disease duration, years, median (IQR, min-max)	10 (10) (min-max:1–49)
MEVF gene analyses[a], *n* (%)	
M694V mutation	45 (76)
V726A mutation	8 (13.5)
M680I mutation	13 (22)
Characteristics of FMF attacks, *n* (%)	
Fever	52 (71.2)
Peritonitis	59 (80.8)
Pleuritis	38 (52)
Arthritis	32 (43.8)
Skin rash (erysipelas-like erythema)	23 (31.5)
Standing myalgia	29 (39.7)
Amyloidosis, *n* (%)	14 (19.2)
Medications	
Colchicine, *n* (%)	73 (100)
Doses 0.5 mg/day	1 (1.3)
1 mg/day	29 (39.7)
1.5 mg/day	25 (34.2)
≥2 mg/day	18 (24.6)
IL-1 antagonists, *n* (%)	
Anakinra	14 (19.2)
Canakinumab	3 (4.1)
Tocilizumab, *n* (%)	1 (1.3)
Disease activity[b], remission, *n* (%)	46 (64)

[a]MEVF gene analyses were available for 59 patients.
[b]Disease activity before the infection was available for 72 patients.

Table 3. COVID-19 characteristics and outcome of FMF patients.

Symptoms, *n* (%)	69 (94.5)
Fever	48 (65.8)
Upper respiratory tract symptoms	46 (63)
Cough	42 (57)
Dyspnea	12 (16.4)
Nausea-vomiting	16 (22)
Diarrhoea	16 (22)
Arthralgia and myalgia	47 (64.4)
Skin findings	3 (4.1)
Outcomes, *n* (%)	
Follow-up	
Outpatient	55 (75.3)
Hospitalization	18 (24.7)
Needing oxygen supplementation	9 (12.3)
ICU admission	3 (4.1)
Complications[a]	5 (6.8)
Mortality	1 (1.4)

[a]Complications were ARDS, myocarditis, acute renal failure, and pericarditis.

including antiviral drugs (favipiravir 75.3% and oseltamivir 8.2%), hydroxychloroquine (17.8%), glucocorticoids (11%), antibiotics (macrolide, fluoroquinolone, and piperacillin-tazobactam; 11%), low-molecular-weight heparin (20.5%), and convalescent plasma (1.4%). Ninety per cent of patients adhered to colchicine, and 85.7% of patients who were on anakinra continued their treatment throughout the COVID-19 course. The vast majority of individuals (75.3%) had outpatient follow-up, and 18 patients were hospitalized for COVID-19. Nine patients who were admitted to the hospital required respiratory support, three of whom developed ARDS and needed intensive care unit (ICU) care for invasive mechanical ventilation and high-flow oxygen. Two patients who developed ARDS had amyloidosis and chronic kidney disease and were on IL-1 antagonist treatment while non-adherent to colchicine treatment. Both patients needed invasive mechanical ventilation. Apart from ARDS, other complications observed in patients were acute renal failure, pericarditis, and myocarditis. The patient who developed acute renal failure had been under renal transplantation due to amyloidosis and adhered to colchicine before the infection. The patient with pericarditis was followed as an outpatient and was non-adherent to colchicine. The only died patient was an 87-year-old male with amyloidosis and chronic kidney disease who developed ARDS and lost in the ICU. During the COVID-19 course of this patient, colchicine was discontinued, while anakinra was continued. Consequently, the mortality rate of COVID-19 in our study was found to be 1.4% among FMF patients. There were only two patients vaccinated for COVID-19 in the study. Both patients were followed as outpatients, and any complications related to COVID-19 were not observed in these patients.

The comparison of patients concerning hospitalization displayed that the male gender was substantially more frequent, and the median age was significantly higher in inpatients than in outpatients (male gender 77.8% vs 25.8%, $p < .001$; median age 39.5 vs 32 years, $p = .043$). Similarly, male gender and elderly patients did require more hospitalization for respiratory support than young and female counterparts ($p = .02$ for both, Table 3). Besides these, the clinical features of FMF were similar in both outpatient and hospitalized patient groups (Table 4). Non-adherence to colchicine before the infection was more frequent in patients requiring oxygen support (33%) in contrast to patients without oxygen support (6.3%) ($p = .03$). The risk factors for hospitalization for oxygen support were determined as male gender [OR: 7.167 (95% CI: 1.368–37.535)], greater age [OR: 1.067 (95% CI: 1.016–1.121)], and non-adherence to colchicine treatment before COVID-19 course [OR: 7.5 (95% CI: 1.348–41.722)] increased the risk of respiratory support.

The flare of FMF attacks after COVID-19 infection

The information about the flare of FMF attacks in the following month after COVID-19 infection was obtained from 66 patients. One-third of the patients had reported attacks, and 15 (68.2%) of them were not in remission before COVID-19. The patterns of triggered attacks in patients at the post-infection period were fever ($n = 3$), peritonitis ($n = 10$), pleuritis ($n = 1$), transient arthritis ($n = 5$), chronic knee mono-arthritis ($n = 1$), protracted febrile myalgia ($n = 1$), and multi-site flare-up ($n = 4$). In addition, 15 out of 25 patients (60%) who were not in remission had triggered attacks compared to patients in remission ($p < .001$). Regarding FMF treatment, attacks were reported by 2 out of 16 patients (12.5%) on IL-1 antagonists compared to 20 out of 50 patients (40%) who were not taking these agents ($p = .042$). No clear benefit of colchicine use was identified by considering the adherence profile of patients ($p = .65$). Besides, one patient who was vaccinated for COVID-19 4 months prior to infection had a pleuritis attack after the infection. The assessment of risk factors for the flare of FMF revealed that active disease before the infection was the only risk factor for FMF attacks after COVID-19 [OR: 7.286 (CI: 2.328–22.805)] (Table 5).

Table 4. The comparison of baseline characteristics of patients according to hospitalization for respiratory support and risk factors of hospitalization for oxygen support.

	Hospitalization for oxygen support			Risk factors for hospitalization/oxygen support
	Yes, *n* (%), *n* = 9	No, *n* (%), *n* = 64	*p* value	OR (95% CI)
Age, median (IQR)	50 (28)	33.5 (14)	.02	1.067 (1.016–1.121)
Gender, male	7 (77.8)	21 (32.8)	.02	7.167 (1.368–37.535)
Active smoking	1 (11.1)	19 (29.7)	.43	0.296 (0.035–2.534)
Comorbidity	7 (77.8)	26 (40.6)	.69	5.115 (0.984–26.602)
Hypertension	1 (11.1)	8 (12.5)	1.0	0.875 (0.096–7.952)
Diabetes mellitus	1 (11.1)	2 (3.1)	.33	3.875 (0.315–47.722)
Cardiovascular disease	1 (11.1)	1 (1.6)	.23	7.875 (0.448–138.581)
Kidney failure	2 (22.2)	4 (6.3)	.15	4.286 (0.661–27.785)
Spondyloathritis	2 (22.2)	10 (15.6)	.63	1.543 (0.279–8.532)
AA amyloidosis	3 (33.3)	11 (17.2)	.36	2.409 (0.521–11.131)
M694V mutation	5 (83.3)	40 (76.9)	1.0	1.500 (0.159–14.116)
Use of IL-1 antagonists	3 (33.3)	14 (21.9)	.43	1.786 (0.396–8.062)
Colchicine non-adherence before the infection	3 (33.3)	4 (6.3)	.03	7.5 (1.348–41.722)
FMF in remission before COVID-19	8 (88.9)	39 (60.9)	.24	0.223 (0.026–1.922)

Table 5. Risk factors for the flare of FMF attacks after COVID-19.

	OR	95% CI lower	95% CI upper	*p* value
Male gender	0.902	0. 303	2.690	.854
Age	0.989	0.948	1.031	.595
Comorbidity	1.444	0.516	4.043	.484
M694V mutation	0.711	0.192	2.630	.609
Active disease before the infection	7.286	2.328	22.805	.001
Dose of colchicine treatment				
1 mg/day	0.614	0.209	1.803	.375
1.5 mg/day	0.725	0.235	2.236	.576
2 mg/day	0.321	0.102	1.008	.052
Use of IL-1 antagonists	0.214	0.044	1.047	.057
Colchicine non-adherence before the infection	0.371	0.041	2.291	.380
Outcomes				
Hospitalization	1.275	0.394	4.123	.685
Respiratory support	1.579	0.321	7.769	.574

Discussion

In our study, 73 FMF patients with COVID-19 were evaluated. All patients were under colchicine treatment, and 23% of patients were under IL-1 antagonist treatment. Over the course of COVID-19, 90.4% of patients adherent to colchicine and 85.7% of patients who were on anakinra continued their treatment. Almost all patients had typical symptoms of COVID-19.

Dysregulated and overreacting innate immune system is the hallmark of FMF; hence it has been suggested that FMF patients might have a higher incidence of severe disease and worse outcomes in COVID-19 [20]. A previous retrospective cohort study evaluating a small number of FMF patients with COVID-19 showed that 23.5% of patients were hospitalized, and the mortality rate was 2.9% [21]. Another small study from France reported the hospitalization rate of 25%, and 11% of patients developed ARDS requiring ICU admission [22]. Similarly, the multicenter study including 59 FMF patients with COVID-19 reported 20% hospitalization, 6.7% oxygen support, and 3.4% complication rate. Older age was found to be associated with COVID-19-related hospitalization, while FMF-related features were not related to worse outcomes [23]. A recent study revealed that the incidence of hospitalization and disease outcomes in FMF inpatients were not different from that of non-FMF inpatients [24]. We found 24.7% hospitalization, 12.3% respiratory support, 4.1% ICU admission, 6.8% complication, and 1.4% mortality rate in our large FMF cohort, consistent with previous studies. Our study demonstrated that older age and male gender had a significantly higher need of hospitalization. Moreover, the study displayed non-adherence to colchicine treatment before COVID-19 as an additional risk factor for respiratory support requirements.

When considering underlying immunopathologic defects in rheumatologic diseases, disease activity might play a substantial role in response to COVID-19 and influence the outcomes. The physician-reported registry with a large number of patients with rheumatologic disorders confirmed that high disease activity was an independent risk factor for the COVID-19-related death. However, autoinflammatory diseases like FMF were not evaluated in this study [25]. The recent research assessing the impact of COVID-19 on FMF disease revealed no association between disease severity and COVID-19-related hospitalization [23]. Two-thirds of patients were in complete remission before the infection in our study, and we did not find an association between remission and worse outcomes.

The impact of COVID-19 on FMF attacks and complications has not been reported yet, particularly in those who already had disease-related complications such as accelerated amyloidosis and kidney failure. SARS-CoV-2 infection can induce the production of cytokines, including IL-1 family, inflammasome activation, and eventually lead to cytokine storm, which might trigger the attacks of FMF and even induce amyloid storm in patients with amyloidosis [8, 11–13]. Our study displayed that one-third of patients had FMF attacks in the following month of COVID-19. Also, the increase in the frequency of attacks was markedly increased in patients with active disease as expected. Besides, the flare of FMF attacks was more prominent in patients, not on IL-1 antagonists. The pattern of attacks after the COVID-19

was congruent with typical attacks like peritonitis, pleuritis, and fever. However, infrequent attacks, pericarditis, chronic mono-arthritis, and protracted febrile myalgia were observed in some of the patients right after the COVID-19 [10]. The observed complications of COVID-19 in our FMF patients were ARDS, acute renal failure, myocarditis, and pericarditis. Two-thirds of patients who developed complications, particularly ARDS and acute renal failure, had amyloidosis. One of the amyloidosis patients was deceased soon after getting infection despite the use of anakinra, but we could not ascertain whether the cause was the amyloid storm.

The current genetic research evaluated pyrin amino acid sequences from different species. Bat and pangolin accepted that reservoir and intermediate hosts for SARS-CoV-2 had FMF associated with pyrin mutations (V726 and R761H). On the other hand, prevalent mutations, such as M680I and M694V, were not detected in these species [26]. This evidence leads to the idea whether some MEVF gene mutations could be responsible for the severity and outcomes of COVID-19 or not. In our study, the most frequent mutation was M694V, with 51% homozygous. There was no relationship between the worse outcomes of COVID-19 and the presence of M694V mutation or homozygous allele mutation.

This study has some limitations. First, it is a cross-sectional study and has no control group. Second, because of the small size of worse outcomes related to COVID-19, such as respiratory failure and mortality, we could not determine FMF-related adverse prognostic factors. Despite all limitations, the major strength of this study is possessing the highest number of FMF patients with COVID-19 in the literature and the assessment of the outcome of background disease, FMF, after the infection.

Conclusions

The mortality rate, hospitalization, need for oxygen support, and complication rates in FMF with COVID-19 were compatible with previous reports. FMF patients with COVID-19 have similar clinical features and outcomes as the general population. FMF genetic and phenotypic features do not influence worse outcomes in COVID-19. Older age and male gender are risk factors for the hospitalization of FMF patients with COVID-19 like the general population. In addition, colchicine non-adherence increases the risk of hospitalization for oxygen support. A significant proportion of FMF patients experience attacks after COVID-19. The dysregulation of the innate immune system in FMF might not be a risk factor for severe COVID-19; however, FMF patients must be followed closely for the occurrence of rare but life-threatening complications of FMF after COVID-19, which are curable with the prompt use of IL-1 antagonists.

Conflict of interest

None declared.

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Ethics approval and consent to participate and for publication

This study was approved by the Ministry of Health and Gazi University Hospital Ethics Committee (protocol number: 322, 29/03/2021) and followed the guidelines from Helsinki Declaration. All patients signed the informed consent, including consent for publication.

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