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Evaluation of IL-1β, IL-18 and Caspase-1 Levels in Familial Mediterranean Fever Patients with Attack and Remission Period

Ailesel Akdeniz Ateşi Hastalarında Atak ve Remisyon Döneminde Serum IL-1β, IL-18 ve Kaspaz-1 Düzeylerinin Değerlendirilmesi

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Abstract

Background: In the pathogenesis of the Familial Mediterranean Fever (FMF) disease, cytokines play important roles in the inflammation of the serous membranes. In this study, we aimed to investigate the relationship of IL-1β, IL-18 and caspase-1 with disease severity scores and acute-phase reactants (APR) in FMF

Material and Method: Sixty patients diagnosed with FMF according to Tel-Hashomer criteria were divided into two groups as attack and attack-free period. Serum cytokines and caspase-1 levels were examined by the ELISA method in 60 patients and 30 healthy volunteers, and the relationship between APR and disease activity was investigated.

Results: FMF attack patient's levels of IL-1β (p=0.001), IL-18 (p=0.043) and caspase-1 (p=0.021) were increased as compared to healthy individuals. There was also a positive relation between IL-1β levels and disease severity as well as acute-phase reactants of attack patients. In FMF remission patients, while a trend towards increased serum IL-1β (p=0.075) and IL-18 (p=0.516) levels were noted, it did not reach statistical significance. However, a borderline difference was observed in the caspase-1 (p=0.049) levels of remission as compared to healthy individuals. In addition, we found no relationship between IL-1β, IL-18 and caspase-1 levels and clinical parameters in remission patients.

Conclusion: The correlation of IL-1β with disease severity supports inhibition of IL-1β activity would provide a therapeutic benefit to patients with FMF. It further suggests that the caspase-1 can serve as a useful marker not only during the attack but also in the remission period, and provides a useful clue for the diagnosis and treatment of the disease.

Keywords: Autoinflammatory diseases, Familial Mediterranean fever, pro-inflammatory cytokines, caspase-1

Öz

Giriş: FMF hastalığının patogenezinde sitokinler, seröz membranların iltihaplanmasında önemli rol oynarlar. Bu çalışmanın amacı, atak ve remisyon döneminde olan FMF hastalarında, serum IL–1β, IL-18 ve kaspaz-1 serum düzeylerinin hastalık şiddeti ve akut faz cevabı ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Tel-Hashomer kriterlerine göre FMF tanısı almış 60 hasta atak ve remisyon dönemi olarak iki gruba ayrıldı. 60 FMF hastasının ve 30 sağlıklı bireyin serum sitokin düzeyleri ELISA yöntemi ile incelendi ve akut faz reaktanları ve hastalık şiddeti ile ilişkisi araştırıldı.

Bulgular: FMF atak hastalarının IL-1β (p=0.001), IL-18 (p=0.043) ve kaspaz-1 (p=0.021) düzeyleri, sağlıklı bireylere göre artış gösterdi. FMF atağı olan hastaların IL-1β seviyeleri ile hastalık şiddeti ve akut-faz cevabı arasında pozitif bir ilişki olduğu gözlemlendi. Remisyon dönemi hastalarının serum IL-1β (p=0.075) ve IL-18 (p=0.516) seviyelerinde artışa doğru bir eğilim kaydedilirken, sadece kaspaz-1 (p=0,049) düzeylerinde bir farklılık gözlemlendi. Bununla birlikte, FMF remisyon hastalarında IL-1β, IL-18 ve kaspaz-1 seviyeleri ile klinik parametreler arasında bir ilişki bulunamadı.

Sonuç: Bu çalışmada, IL-1β ile hastalık şiddeti arasındaki korelasyonun, IL-1β'nin inhibisyonun FMF'li hastalara terapötik bir fayda sağladığını desteklemektedir. Ayrıca, kaspaz-1'in sadece atak döneminde değil, ataklar arası dönemde de yararlı bir biyobelirteç olarak hizmet edebileceğini, hastalığın tanı ve tedavisi için yararlı bir ipucu sağlayabileceğini göstermektedir.

Anahtar Kelimeler: Otoinflamatuar hastalıklar, Ailevi Akdeniz ateşi, pro-inflamator sitokinler, kazpaz-1

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INTRODUCTION

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease with autosomal recessive inheritance.[1] FMF is caused by mutations of the Mediterranean Fever (MEFV) gene, coding a protein named pyrin. It is expressed mainly in myeloid cells, is implicated in inflammation by the activation of caspase-1, which is responsible for the maturation of IL-1β and IL-18.[2] The deficiency in the amount or activity of pyrin results in an inability to suppress and/or inhibit the inflammatory processes.[3] In the pathogenesis of the FMF disease, cytokines play important roles in the inflammation of the serous membranes. The cytokines that are produced throughout and took part in the inflammatory procedure are the principal stimulators of the manufacture of acute-phase proteins such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen in FMF.[4]

IL-1β and IL-18 are members of the interleukin (IL) -1 family and have long been recognized as a potent inflammatory mediator.[5] IL-1β is one of the key cytokines in the mediation of inflammation in autoinflammatory diseases.[6] IL-1β mainly functions to stimulate leukocyte activation and induces fever and acute-phase proteins at high levels which trigger the systemic inflammatory responses. IL-1β activation is triggered by an intracellular sensor that activates the inflammasome to cleave pro-IL-1β into its active form by caspase-1.[7,8] The IL-1β levels are known to be increased in Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID).[9] Several studies also report that increased IL-1β levels in FMF attack patients.[10,11] The results of these studies suggest that IL-1β values seem to correlate with CRP levels and IL-1β could be used in the diagnosis of an acute attack and monitoring the response to the treatment.[10]

In a similar manner of IL-1β, IL-18 is produced as a pro-peptide that needs to be cleaved by caspase-1 after activation of the inflammasome.[12] IL-18 precursor is present and constitutively expressed in monocytes, macrophages and proximal tubular epithelial cells.[13] The IL-18 levels are known to be increased in various pathologic conditions, such as inflammatory arthritis, inflammatory bowel disease, and systemic lupus erythematosus.[14] Serum IL-18 concentrations can discriminate patients with FMF from healthy controls. However, IL-18 has been distinctly evaluated for its potential to discriminate disease activity in FMF. Interestingly, while several studies showed that disease severity increases with IL-18 in the pathogenesis of FMF disease, others have not observed a relationship between IL-18 and disease activity.[15-17]

Caspase-1 is a member of a family of nine cysteine proteases and mediates programmed cell death by promoting the cleavage of critical intracellular proteins upon apoptotic activation.[18] Caspase-1, however, seems to be uniquely involved in participating in the inflammatory response by cleaving the precursors of IL-1 beta, IL-18 and IL-33.[5] Pyrin is expressed mainly in neutrophils, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts (mostly in the innate immune system cells) and regulates caspase-1 activation.[1,19,20] These studies indicate that inhibition of the interaction between pyrin and caspase-1 leads to an increase in caspase-1 activity and a subsequent increase in IL-1β secretion in FMF disease.[21]

Furthermore, several studies have been reported the activation of cytokine networks during FMF attacks. However, information on the regulation of inflammation by cytokines in FMF is limited and contradictory especially during the FMF attack and remission period. Therefore, the present study was performed to determine the IL–1β, IL-18, caspase-1 as indicators of FMF.

MATERIAL AND METHOD

Study Populations

In this study, whole blood and serum samples were obtained from FMF patients who came to the physical therapy and rehabilitation and emergency department of Tokat Gaziosmanpasa University Hospital. Sixty FMF patients were divided into two groups, FMF remission and attack. Twelve male and eighteen female patients, aged 20-57 years, were evaluated only during a remission period (defined as being free of attacks for at least 2 weeks based on clinical (fever, abdominal pain, and arthritis) and laboratory findings [high sensitive C-reactive protein (hs-CRP), fibrinogen, and white blood cell (WBC) count). Fifteen male and 15 female attack period patients, aged 19-56 years, were determined based on clinical (fever, abdominal pain, arthritis) and laboratory findings (high levels of fibrinogen, white blood cell (WBC) counts and erythrocyte sedimentation rate (ESR)). Eight male and twenty-two female healthy individuals, aged 20-56 years were included as a control group.

Clinical Classifications

FMF patients were diagnosed according to the Tel-Hashomer diagnostic criteria, requiring the presence of at least 1 of 4 major criteria, 2 of 5 minor criteria, or 1 minor criterion plus 5 of all 10 supportive criteria for definite FMF diagnosis.[22] All patients were being treated with colchicine (1–2 mg/day), were identified. Epidemiologic data (including sex, consanguinity of parents, familial history, and age of onset of inflammation signs) and main clinical data (including fever; thoracic, abdominal and articular; duration; the presence of amyloidosis; and response to colchicine) were recorded.

Laboratory Assay

A sample of 8 ml fasting venous blood was taken in the morning from all participants. The serum was obtained by centrifugation of blood samples at 3000 rpm for 15 min at 4°C. Afterward, serum samples were stored at -80°C until further analyzed.

Hs-CRP, fibrinogen, and WBC counts were measured within less than 1 hr after the sampling. Hs-CRP levels were determined by the nephelometric method (Beckman Array 360 Protein System, Minnesota, Brea). Fibrinogen levels were measured by the clotting time method (Beckman Coulter, Inc., Fullerton, CA), and leukocytes were determined with an automatic hematology analyzer (Beckman Coulter, Inc., Fullerton, CA).

The enzyme-linked immunosorbent assay (ELISA) technique was applied to determine the serum concentrations of IL-1β, IL-18 and caspase in 60 patients and 30 controls. The optical density was determined using an enzyme-linked immunoassay kit according to the manufacturer protocol (BT Lab., CHINA) The spectrophotometric reading was performed by a Multiskan GO Microplate Spectrophotometer (Thermo Scientific, USA).

Statistical Analysis

The Shapiro-Wilk test was used to check the normal distribution of the data. Skewed variables were expressed as median with interquartile range. Since the variables did not show normal distribution, nonparametric tests, which were more suitable than statistical tests, were used. Mann–Whitney U test was used for nonhomogenous distributed data. Mann-Whitney U test was used in a comparison of patients with healthy volunteers as well as in binary group comparisons. Spearman's rank correlation coefficient test was used to explore the correlations between the cytokines and clinical characteristics. All statistical analyses were performed by SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) and graphs were generated using GraphPad Prism version 8.3.0 (GraphPad Software, Inc., CA, USA). A two-tailed P-values in the figures and tables are indicated as follows: (*: p≤0.05; **: p≤0.01, ***: p≤0.001).

Ethics approval

This research study was approved by Tokat Gaziosmanpasa University clinical research ethics committee (#19-KAEK-164) and it was planned and conducted by the provisions of the Helsinki Declaration. All participants gave informed written consent to participate in the study.

RESULTS

The baseline clinical characteristics of FMF attack and remission patients were summarized in **Table 1**. Among FMF attack patients, 20.0% (6/30) were heterozygotes, 36.6% (11/30) were homozygotes, 30.0% (9/30) were compound heterozygotes and no mutation was found in 13.3% (4/30). In FMF remission patients, there were 36.6% (11/30) heterozygotes, 13.3% (4/30) homozygotes, 33.3% (10/30) compound heterozygotes and no mutation was found in 16.6% (5/30). The mean age at diagnosis of FMF attack (19.0±9.3) and remission (28.6±13.2), (p=0.002). Disease severity calculated by defined Pras et al.[23] and the pras score of FMF attack patients was significantly higher than FMF remission (p=0.009).

Table 1. Baseline characteristics of patients with FMF.

	FMF (during attack) (n=30)	FMF (attack free) (n=30)
Age at diagnosis (years)	19.0±9.3*	28.6±13.2
Duration of illness (years)	12.2±9.0	10.7±6.8
BMI	24.2±4.5*	27.1±3.9
Pras score	7.8±2.5*	6.8±2.1
Dose of colchicine (mg/day)	2.8±0.6	2.9±0.6
Family history of FMF, n (%)	16 (53.3)	11 (36.6)
Fever, n (%)	22 (73.3)*	16 (53.3)
Abdominal pain, n (%)	26 (86.6)	23 (76.6)
Chest Pain, n (%)	14 (46.6)	10 (33.3)
Joint pain, n (%)	18 (60)	20 (66.6)
Arthritis/arthralgia, n (%)	13 (43.3)	9 (30)
Myalgia, n (%)	9 (33.3)	10 (33.3)
Splenomegali	1 (3.3)	0
Type of mutation		
Heterozygote, n (%)	6 (20.0)	11 (36.6)
Homozygote, n (%)	11 (36.6)	4 (13.3)
Compound heterozygote, n (%)	9 (30)	10 (33.3)
Wild type, n (%)	4 (13.3)	5 (16.6)

Data are presented as the mean±SD for continuous variables. P values were obtained using a Mann-Whitney U test. (*: p≤0.05) : significance between attack and remission in FMF patients.

In addition, the baseline laboratory characteristics of FMF attack, remission patient groups and healthy individuals were presented in **Table 2**. Accordingly our results, WBC, neutrophil, CRP and fibrinogen measurements were significantly higher in FMF attack compared to healthy individuals (p<0.0001, p<0.0001, p<0.0001, p=0.026, resp.). There was also a significant differences in WBC, neutrophil, CRP and fibrinogen levels between FMF attack and remission (p<0.0001, p<0.0001, p<0.0001, p=0.036, resp.). However, the NLR ratio was higher in both FMF attack and remission than in healthy individuals (p<0.0001, p<0.0001, resp.). When we compared the clinical parameters of remission and control groups, we also found that ESR (p=0.0216) was significantly higher in remission patients..

In FMF attack patients serum concentrations of IL-1β (p=0.001), was significantly higher than the control group. And also, FMF attack patient's levels of IL-18 (p=0.043), caspase-1 (p=0.021) were statistically altered compared to healthy individuals (**Figure 1**). The results suggest that serum levels of IL-1β and caspase-1 are correlating together in FMF attack. In FMF remission patients, while a trend towards increased serum IL-1β (p=0.075) and IL-18 (p=0.516) levels were noted, it did not reach statistical significance. However, a borderline difference was observed in the caspase-1 (p=0.049) levels of remission according to control (**Figure 1**).

In addition, we performed a Spearman correlation analysis to evaluate the relationship of these cytokines among themselves and patients clinical findings. There was a correlation between IL-1β and acute phase reactant ESR (r=0.710, p=0.01), CRP (r=0.550, p=0.05, resp.) in FMF attack patients. We also observed a significant correlation between IL-1β, lymphocyte and pras score (r=-0.500, p=0.008, r=0.570, p=0.004) in FMF attack patients (**Table 3**). There was no relationship between IL-1β, IL-18 and caspase-1 with clinical parameters of FMF remission patients.

Table 2. Comparison of parameters among patients and healthy controls.

Comparison of parameters	Attack (n=30)	Remission (n=30)	Control (n=30)
WBC 10^3/mL	10.8 (5.2-26.9)***†††	7.3 (4.3-11.9)	6.8 (4.3-11.3)
Lymphocyte	1.9 (0.9-4.8)	2.1 (0.9-3.1)	2.2 (1.2-5.0)
Neutrophil	8.2 (3.0-24.5)***†††	4.5 (1.6-9.8)	3.9 (2.0-6.5)
NLR, %	3.8 (1.1-26.9)***†††	0.5 (0.09-1.3)***	1.4 (1.0-4.8)
ESR, mm/h	14.5 (9.0-65.0)	13.0 (5.0-43.0)*	11.0 (2.0-49.0)
CRP, mg/L	25.4 (0.1-199.3)***†††	2.2 (0.2-42.1)	1.8 (0.1-12.0)
Fibrinogen	328.0 (233.0-463.0)*†	258.3 (171.4-464.0)	272.0 (183.0-399.0)
IL-1β, pg/mL	11750.0 (3178-25054.0)***	4063.0 (1210.0-18029.0)	2117.0 (1254.0-4180.0)
IL-18, ng/mL	13.6 (2.4-140.9)*	4.2 (2.6-139.9)	5.3 (0.1-14.64)
Caspase-1, ng/mL	3.8 (1.0-60.6)*	1.9 (1.1-50.8)*	1.1 (0.7-4.7)

Median (interquartile range) or minimum-maximum levels are shown. *: p≤0.05; **: p≤0.01, ***: p≤0.001 significance between FMF patients and healthy controls. NLR: neutrophil to lymphocyte ratio; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 3. Correlation of IL-1β, IL-18 and Caspase-1 serum levels with continuous variables in FMF patients and healthy controls.

Continuous Variables	Attack						Remisson						Control					
	IL-1β		IL-18		Caspase-1		IL-1β		IL-18		Caspase-1		IL-1β		IL-18		Caspase-1	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
WBC	0.12	0.69	0.20	0.58	0.36	0.22	-0.07	0.86	0.43	0.21	0.14	0.71	0,07	0,87	-0,41	0,25	0,19	0,61
Lymphocyte	-0.50	0.08*	-0.02	0.97	-0.05	0.87	0.21	0.55	0.34	0.33	0.05	0.90	-0,33	0,35	-0,28	0,43	0,22	0,53
Neutrophil	0.21	0.49	-0.02	0.97	0.30	0.31	-0.17	0.65	0.21	0.56	0.04	0.92	0,14	0,71	0,04	0,92	-0,08	0,84
NLR	0.43	0.15	0.09	0.81	0.05	0.87	0.14	0.70	0.12	0.75	-0.05	0.90	0,49	0,15	0,32	0,37	-0,24	0,51
ESR	0.71	0.01**	0.17	0.64	0.15	0.65	0.16	0.68	0.07	0.86	0.08	0.83	0,02	0,95	-0,71	0,03*	-0,20	0,58
CRP	0.55	0.05*	0.09	0.81	-0.07	0.81	-0.55	0.10	-0.38	0.28	-0.52	0.12	0,59	0,08*	-0,04	0,92	0,08	0,84
Pras Score	0.57	0.04*	0.17	0.63	0.43	0.14	-0.43	0.21	-0.26	0.46	-0.33	0.35						

Statistically significant; a Spearman's correlation between variables, *: p≤0.05; **: p≤0.01.

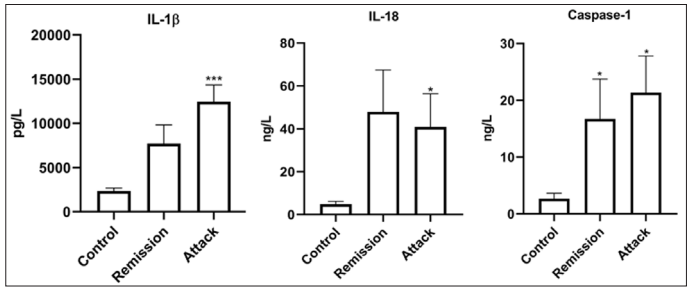

Figure 1. Comparison of serum IL-1β, IL-18 and Caspase-1 in FMF attack/remission patients and control group. Graphed data with error bars denoting standard error of the mean (SEM). Statistical significance was calculated using SPSS-Mann-Whitney U test. (*: p≤0.05; **: p≤0.01, ***: p≤0.001).

DISCUSSION

In the present study, FMF attack patient's disease severity was higher than the remission group (**Table 1**). In addition, WBC, neutrophil, CRP and fibrinogen measurements were increased in FMF attack compared with remission and control group. However, the NLR ratio was higher in both FMF attack and remission than in control (**Table 2**). And also, FMF attack patient's levels of IL-1β, IL-18 and caspase-1 were increased compared to healthy individuals (**Figure 1**). We also found a positive correlation between IL-1β and disease severity, neutrophil, ESR and CRP levels in FMF attack patients (**Table 3**). In FMF remission patients NLR and ESR measurements were higher compared to control. Furthermore, an increase was observed in remission patients IL-1β, IL-18 and caspase-1 levels compared to control, a significant difference was observed only caspase-1 level. We did not observe a relationship between IL-1β, IL-18 and caspase-1 levels and inflammatory markers including CRP, ESR in FMF remission patients.

In the literature, Notarnicola et al.[24] have investigated the transcriptional cytokine expression levels of TNF-α, IL-1β, IL-6 and IL-8 and found higher cytokine expression in FMF remission than control. Yildirim et al.[10] also found higher serum IL-1β levels in patients with FMF than control subjects. Experimental and clinical evidence support the prominent role of IL-1β in the pathogenesis of FMF. Evidence for the role of IL-1β arises from clinical recovery after IL-1β blockade in FMF pathogenesis.[25,26] However, parameters that trigger attacks are still under investigation. Here, we showed that the association of IL-1β with disease severity and acute-phase proteins during the attack period. It is known that acute-phase reactants such as CRP and ESR may increase in many diseases,[27] so they are not sufficient to evaluate FMF disease. Therefore, there is a need for new pathways that can increase or contribute to the reduction of disease severity of FMF attack. In our study, increased IL-1β level in FMF attack patients was positively correlated with disease severity, neutrophil, ESR and CRP (**Table 3**). It was reported that increased levels of inflammatory mediators such as ESR, CRP, and SAA in FMF attacks.[18] Korkmaz et al.[4] reported high APR in 34% of the remission intervals. These findings support that neutrophils were the source of IL-1β in the blood which acts the disease progression and increasing CRP and ESR levels mediate this progress.[26] The correlation of IL-1β with disease severity supports inhibition of IL-1β activity would provide a therapeutic benefit to patients with FMF.

Herein, we also observed an increase in IL-18 level during the attack period of FMF disease, we did not observe any relationship between IL-18 and disease severity or acute-phase response both attack and remission. Only a few studies have investigated serum IL-18 levels in patients with FMF, the results of which have demonstrated higher IL-18 levels in FMF patients compared to healthy controls.[13,28] The studies by Haznedaroglu et al.[15] and Simsek et al.[16] compared IL-18 levels and disease activity, found no relationship with IL-18. However, of these, Gohar et al.[17] observed the correlation with clinical disease activity and IL-18 in patients with FMF attack and remission. These results show that IL-18 plays a distinct role in the disease progression of FMF patients. Although longer-term prospective studies are needed to confirm this.

Finally, there was an increase in caspase-level in FMF attack and remission patients, but we did not observe a correlation with clinical parameters. Some studies demonstrated that pyrin itself can either inhibit or accentuate caspase-1 activity through the interaction of its N-terminal death-fold with ASC, a key molecule in the inflammasome.[12,29] Yu et al.[30] demonstrated that activated pyrin interacts with ASC and activates caspase-1 and subsequently leads to active IL-1β secretion. Neutrophils from patients with FMF secreted IL-1β and showed increased caspase-1 activity in vitro.[31,32] Consequently, overproduction of IL-1β by caspase-1 is the main cause of episodic fever and inflammatory findings in FMF.[33] Our results suggest that the elevation of caspase-1 levels may be important in monitoring subclinical inflammation of remission period in FMF patients. These findings may also contribute to the evaluation of FMF and IL-1β and caspase-1 cytokine levels together in the diagnosis of the disease.

CONCLUSION

In summary, our results support the importance of IL-1β, IL-18 and caspase-1 as a disease activity marker and show that longitudinal examination of pro-inflammatory cytokines may contribute to better follow-up of FMF patients.

Limitations of study

The results of this study are subjected to some limitations. First, this study was not based on longitudinal observations but was conducted with a cross-sectional design. Second, it is a single-center study with a relatively small sample size, which might underestimate or overestimate the relationship between biomarkers and renal involvement due to FMF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The present study was approved by the ethical review committee of the Tokat Gaziosmanpasa University clinical research ethics committee date 2018 numbered 19-KAEK-164.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Migita K, Asano T, Sato S, Koga T, Fujita Y, Kawakami A. Familial Mediterranean fever: overview of pathogenesis, clinical features and management. Immunol Med. 2018;41(2):55-61.
2. Van Gorp H, Saavedra PH, de Vasconcelos NM, et al. Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in Pyrin inflammasome activation. Proc Natl Acad Sci U S A. 2016;113(50):14384-9.
3. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med. 1967;43(2):227-53.
4. Korkmaz C, Ozdogan H, Kasapçopur O, Yazici H. Acute phase response in familial Mediterranean fever. Ann Rheum Dis. 2002;61(1):79-81.
5. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018;281(1):8-27.
6. Skendros P, Chrysanthopoulou A, Rousset F, et al. Regulated in development and DNA damage responses 1 (REDD1) links stress with IL-1β-mediated familial Mediterranean fever attack through autophagy-driven neutrophil extracellular traps. J Allergy Clin Immunol. 2017;140(5):1378-87.e13.
7. Hesker PR, Nguyen M, Kovarova M, Ting JP, Koller BH. Genetic loss of murine pyrin, the Familial Mediterranean Fever protein, increases interleukin-1β levels. PLoS One. 2012;7(11):e51105.
8. Grandemange S, Aksentijevich I, Jeru I, Gul A, Touitou I. The regulation of MEFV expression and its role in health and familial Mediterranean fever. Genes Immun. 2011;12(7):497-503.
9. Lorente-Sorolla C, Netea MG, Ballestar E. "Epigenetics in Autoinflammation", Textbook of Autoinflammation, Springer International Publishing, 2019, ss. 49–60.
10. Yildirim K, Uzkeser H, Keles M, et al. Relationship between serum interleukin-1beta levels and acute phase response proteins in patients with familial Mediterranean fever. Biochem Med (Zagreb). 2012;22(1):109-13.
11. A. Akdeniz vd., "Ailevi Akdeniz Ateşi Genetik Özellikleri ve Sistemik Hastalıklarla İlişkisi", 2020.
12. Chae JJ, Wood G, Richard K, et al. The familial Mediterranean fever protein, pyrin, is cleaved by caspase-1 and activates NF-kappaB through its N-terminal fragment. Blood. 2008;112(5):1794-803.
13. Novick D, Kim S, Kaplanski G, Dinarello CA. Interleukin-18, more than a Th1 cytokine. Semin Immunol. 2013;25(6):439-448.
14. Álvarez-Errico D, Vento-Tormo R, Ballestar E. Genetic and Epigenetic Determinants in Autoinflammatory Diseases. Front Immunol. 2017;8:318.
15. Haznedaroglu S, Oztürk MA, Sancak B, et al. Serum interleukin 17 and interleukin 18 levels in familial Mediterranean fever. Clin Exp Rheumatol. 2005;23(4 Suppl 38):S77-S80.
16. Simsek I, Pay S, Pekel A, et al. Serum proinflammatory cytokines directing T helper 1 polarization in patients with familial Mediterranean fever. Rheumatol Int. 2007;27(9):807-811.
17. Gohar F, Orak B, Kallinich T, et al. Correlation of Secretory Activity of Neutrophils With Genotype in Patients With Familial Mediterranean Fever. Arthritis Rheumatol. 2016;68(12):3010-22.
18. Netea MG, van de Veerdonk FL, van der Meer JW, Dinarello CA, Joosten LA. Inflammasome-independent regulation of IL-1-family cytokines. Annu Rev Immunol. 2015;33:49-77.

19. Ozdogan H, Ugurlu S. Familial Mediterranean Fever. Presse Med. 2019;48(1 Pt 2):e61-e76.
20. Manukyan G, Aminov R, Hakobyan G, Davtyan T. Accelerated apoptosis of neutrophils in familial mediterranean Fever. Front Immunol. 2015;6:239.
21. Bozkurt Y, Demir A, Erman B, Gül A. Unified Modeling of Familial Mediterranean Fever and Cryopyrin Associated Periodic Syndromes. Comput Math Methods Med. 2015;2015:893507.
22. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997;40(10):1879-85.
23. Pras E, Livneh A, Balow JE Jr, et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet. 1998;75(2):216-9.
24. Notarnicola C, Didelot MN, Seguret F, Demaille J, Touitou I. Enhanced cytokine mRNA levels in attack-free patients with familial Mediterranean fever. Genes Immun. 2002;3(1):43-5.
25. Özçakar ZB, Özdel S, Yılmaz S, Kurt-Şükür ED, Ekim M, Yalçınkaya F. Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. Clin Rheumatol. 2016;35(2):441-6.
26. Soriano A, Verecchia E, Afeltra A, Landolfi R, Manna R. IL-1β biological treatment of familial Mediterranean fever. Clin Rev Allergy Immunol. 2013;45(1):117-30.
27. Hacımustafaoğlu M. "Akut Faz Reaktanları (Eritrosit Sedimentasyon Hızı, CRP) Acute Phase Reactants (Erythrocyte Sedimentation Rate, CRP)", J Pediatr Inf. 2017; 11: 53-5. doi: 10.5578/ced.201701.
28. Wada T, Toma T, Miyazawa H, et al. Longitudinal analysis of serum interleukin-18 in patients with familial Mediterranean fever carrying MEFV mutations in exon 10. Cytokine. 2018;104:143-6.
29. Moghaddas F, Llamas R, De Nardo D, et al. A novel Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis mutation further defines 14-3-3 binding of pyrin and distinction to Familial Mediterranean Fever. Ann Rheum Dis. 2017;76(12):2085-94.
30. Yu JW, Wu J, Zhang Z, et al. Cryopyrin and pyrin activate caspase-1, but not NF-kappaB, via ASC oligomerization. Cell Death Differ. 2006;13(2):236-49.
31. Omenetti A, Carta S, Delfino L, Martini A, Gattorno M, Rubartelli A. Increased NLRP3-dependent interleukin 1β secretion in patients with familial Mediterranean fever: correlation with MEFV genotype. Ann Rheum Dis. 2014;73(2):462-9.
32. Chae JJ, Wood G, Masters SL, et al. The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production. Proc Natl Acad Sci U S A. 2006;103(26):9982-7.
33. Apostolidou E, Skendros P, Kambas K, et al. Neutrophil extracellular traps regulate IL-1β-mediated inflammation in familial Mediterranean fever. Ann Rheum Dis. 2016;75(1):269-77.