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Serum triggering receptor expressed on myeloid cells-1 (TREM-1) levels may be associated with disease activity in patients with familial Mediterranean fever

Ailevi Akdeniz ateşi tanılı hastalarda serum triggering receptor expressed on myeloid cells-1 (TREM-1) düzeyleri hastalık aktivitesi ile ilişkili olabilir

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Abstract

Objective: Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease, which is characterized by self-limited attacks of serositis, fever, and arthritis. Triggering receptor expressed on myeloid cells-1 (TREM-1), a member of the inflammatory immunoglobulin superfamily member, is expressed by neutrophils, monocyte, and macrophages and has a role in promoting inflammatory cascade. The study aimed to evaluate serum soluble TREM-1 (sTREM-1) levels in patients with FMF and compare them according to clinical status.

Methods: A total of 65 FMF patients diagnosed with Eurofever criteria, and 21 healthy controls were enrolled in the study. Patients who were followed in Gazi University Rheumatology Outpatient Clinic were included prospectively and separated into three groups; 1. attack period, 2. remission period, and 3. in remission and have amyloidosis. sTREM-1 levels were assessed from peripheral blood.

Results: Age, sex, duration of disease, and genetic mutations were similar between groups. Patients during the attack period have a significantly higher rate of fever and peritonitis attacks compared to other groups. There was also no significant correlation between the level of sTREM-1 and ongoing inflammation, but have a positive correlation with body mass index and age; also, a negative correlation with Autoinflammatory Disease Activity index score ($p<0.05$).

Conclusion: Serum sTREM-1 levels may have a predictive role in the clinical activity of FMF patients.

Keywords: Familial Mediterranean fever, clinical activity, sTREM-1

Öz

Amaç: Ailevi Akdeniz ateşi (FMF) serosit, ateş ve artrit atakları ile karakterize olan en yaygın monojenik otoenflamatuvar hastalıktır. Enflamatuvar immünoglobulin süper aile üyesinin bir üyesi olan myeloid hücreler-1 (TREM-1) nötrofiller, monosit ve makrofajlar tarafından üretilir ve enflamatuvar kaskadın alevlenmesinde rol oynar. Çalışmada, FMF'li hastalarda serum çözünür TREM-1 (sTREM-1) seviyelerinin değerlendirilmesi ve klinik durum ile karşılaştırılması amaçlanmıştır.

Yöntem: Eurofever kriterleriyle tanı konulmuş olan toplam 65 FMF hastası ve 21 sağlıklı kontrol çalışmaya dahil edilmiştir. Gazi Üniversitesi Romatoloji Kliniği'ni izlenen hastalar prospektif olarak çalışmaya alınmış ve üç gruba ayrılmıştır; 1. atak dönemi, 2. interatak dönem, 3. amiloidoz pozitif hastalarda interatak dönemidir. STREM-1 seviyeleri çalışma grubu üyelerinden alınan periferik kandan alınan serum örneklerinde değerlendirilmiştir.

Bulgular: Yaş, cinsiyet, hastalık süresi ve genetik mutasyonlar gruplar arasında benzerdi. Ayrıca sTREM-1 seviyesi ile devam eden enflamasyon arasında önemli bir korelasyon yoktu, ancak vücut kütle indeksi ve yaşla pozitif bir korelasyon mevcuttu. Ayrıca Otoenflamatuvar Hastalık Aktivite indeksi puanıyla negatif bir korelasyon saptandı ($p<0,05$).

Sonuç: Serum sTREM-1 seviyelerinin FMF hastalarının klinik aktivitesinde öngörücü bir rolü olabilir.

Anahtar Kelimeler: Ailevi Akdeniz ateşi, sTREM-1, klinik aktivite

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Introduction

Familial Mediterranean fever (FMF) is the common hereditary autoinflammatory disease that primarily affects East Mediterranean populations like Turks, Jews, Arabs, and Armenians. Disease is caused by the *MEFV* gene mutations, which encode a protein called pyrin, which has regulatory functions on the innate immune system.[1] Because of the pathophysiological pathway is associated with innate immune system, mechanisms underlying FMF pathogenesis have many immune pathways including intracellular danger sensors, inflammasomes, pyroptosis and NETosis.[1]

Colchicine is an ancient and effective treatment for suppressing clinical activity and ongoing inflammation and decreasing risk of damage.[2] IL-1 antagonists are also effective options for patients who have colchicine resistance and/or intolerance.[3] Disease activity is assessed with frequency, severity, and duration attacks as well as with C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum amyloid A (SAA) levels at attack-free period. AIDAI score was conducted for numeric evaluation of clinical activity of disease and included all clinical parameters listed in the description of activity and ranges between 0-9.[4]

Soluble TREM-1 (sTREM-1) is a member of the immunoglobulin superfamily and is measured in human studies in two forms: soluble and membrane-bound.[5] When a membrane-bound form of sTREM-1 is activated, toll-like receptor-induced cytokines like TNF, IL-1b, IL-6, and IL-8 increase. So sTREM-1 levels propagate the severity of inflammation.[6] As a result, plasma sTREM-1 levels increased in serum and affected regions like pleural fluid, bronchoalveolar lavage, and cerebrospinal fluid.[6,7]

Many studies described the relationship between sTREM-1 levels and the activity of autoimmune diseases. Synovial fluids of patients with RA showed higher sTREM-1 compared to gouty and osteoarthritis.[8] In a murine model of collagen-induced arthritis, decreasing sTREM-1 levels suppressed inflammation of synovial fluid and treated arthritis.[9] Also, in patients with systemic lupus erythematosus, serum sTREM-1 levels were significantly increased and positively correlated with disease activity score and predictive for neuropsychiatric involvement.[10]

sTREM-1 levels were studied at Adult-onset Still disease (AOSD) and FMF from autoinflammatory diseases. sTREM-1 levels were increased in patients with AOSD and were predictive of the chronic course.[11] Also, patients with FMF levels of sTREM-1 were associated with the presence of amyloidosis in two distinct studies.[12,13] The originality of our study originated from that we compared sTREM-1 levels with the clinical activity scores of patients. We hypothesized that serum levels of sTREM-1 may be associated with the clinical activity of FMF.

Materials and Methods

Study Design

The study was a cross-sectional study conducted in the outpatient clinic between March and September 2022. Patients who have been diagnosed with FMF according to Eurofever criteria and above 18 years old were included in the study.[14] Patients who were younger than 18 years old and have other autoinflammatory diseases were excluded. Clinical demographic features, genetic mutations, median levels of serum CRP and ESR levels at attack-free period, and spot urinary excretion of protein/creatinine ratio were recorded. Severity, duration, frequency of attacks, current medications, and colchicine resistance/intolerance were also entered into registry records. The dominant attack type is determined based on the type of attack that the patient experienced most frequently during the entire duration of the disease. All study protocol was compatible with the Declaration of Helsinki. Informed consent was obtained from all participants and kept in study documents. The Local Ethical Committee of Gazi University approved the study (approval number: 622, date: 25.12.2017).

Definition of Clinical Status

Auto-Inflammatory Diseases Activity index (AIDAI) was calculated for all patients to obtain a clinical score.[4] Colchicine resistance is defined as typical attacks of disease which have a frequency of once-a-month and/or high levels of acute phase proteins at an attack-free period for a minimum of 3 months.[15] Damage was assessed with parameters of the Autoinflammatory Disease Damage index like amenorrhea, infertility, joint diseases, chronic renal disease, and insufficiency which are not explained with other reasons.[16]

Laboratory Examinations

Serum venous blood samples were taken from all participants and centrifugated at 3000 rpm for 10 minutes and stored at -80 °C. Blood samples from the attack period were taken within first 6 hours of the attack. Blood sTREM-1 levels were studied by ELISA method via Elabscience- Human Strem-1 (E-EL-H1596) kit and results were expressed as pg/mL.

Statistical Analysis

Results were analyzed with SPSS statistical program 21.0 version. The distribution of all numeric variables was

assessed with one sample Kolmogorov-Smirnov test and all of them showed irregular distribution. Kruskal-Wallis and Mann-Whitney U tests were used according to the number of compared groups. Nominal parameters were compared with chi-square test. Correlations of numeric variables were performed with Pearson's test. P values under 0.05 were accepted as statistically significant.

Results

Table 1 shows all demographic features of the participants. The mean age of the study group was 35.6±11.6 and patients with amyloidosis have a significantly higher mean age (39.7±9.6 years) when compared to other groups (p=0.038). Dominant attack types were peritonitis and fever for patients during the attack period; peritonitis for those at attack-free period and arthritis for patients with amyloidosis. The percentage of fever and peritonitis were significantly different between FMF groups (p=0.025 and p=0.046, in order). Twenty-five patients were treated with only colchicine with maximal tolerable dose (38%), 7 patients were treated with only IL-1 antagonists because of colchicine intolerance (10.7%) and 32 patients were treated with colchicine and IL-1 antagonists because of colchicine resistance (51.3%). Patients treated with IL-1 antagonists were significantly higher in patients with amyloidosis and colchicine dose was lower when compared to patients without amyloidosis because of the restriction of glomerular filtration rate (p=0.002). Most of the patients were in remission respecting to AIDAI score [median: 4 (interquartile range: 3.75)], patients with attack periods were also in remission but have occasional attacks when triggering factors were increased. Ten (15%) patients have high AIDAI score and the distribution between groups was similar.

Plasma sTREM-1 levels were similar between all study groups (p>0.05, Table 2, Figure 1). Patients at attack period and amyloidosis did not show higher levels of sTREM-1 when compared to other groups. Correlation analysis showed a positive correlation of sTREM-1 levels with age (r=0.384, p<0.001) and body mass index (r=0.331, p=0.003); controversially a negative correlation with AIDAI score (r=-0.307, p=0.014). As expected, patients in the attack period had significantly higher levels of CRP and ESR and patients

Table 1. Demographic and clinical properties of the study group

	Patient at attack period (n=16)	Patients at attack-free period (n=30)	Patients with amyloidosis (n=19)	Healthy control (n=21)	p
Age [years, median (IQR)][a]	35 (17)	**28 (15)**	**42 (11.5)**	29.5 (18.8)	**0.038**
Sex (number of patients, female/male)	8/8	15/15	5/14	9/12	0.38
Smoking (number)	7 (43.75)	14 (46.6)	8 (42.1)	6 (28.5)	0.27
Education (number)[b]					
Primary school	2	2	3	1	0.13
Middle school	1	2	3	4	
High school	7	11	5	4	
University	4	15	6	11	
Body mass index [kg/m^2 median (IQR)]	26.6 (9.14)	22.09 (6.65)	21.22 (6.51)	23.25 (4.52)	0.22
Duration of disease [years, median (IQR)]	14 (12.3)	16 (10.5)	20 (14)	-	0.19
Type of attacks [number (%)][d,e]					
Fever	12 (75)	19 (63.3)	6 (31.5)		**0.025**
Peritonitis	12 (75)	24 (80)	9 (47.3)		**0.046**
Pleuritis	6 (37.5)	11 (36.6)	3 (15.7)		0.24
Arthritis	12 (75)	21 (70)	11 (57.8)		0.52
Erysipeal-like erythema	3 (16.7)	5 (16.6)	0	-	0.14
Mutations [number (%)][e]					
M694V	17	28	25		0.92
M680I	4	8	4		
R761H	2	0	0	-	
V726A	1	2	1		
R202Q	1	1	0		
F479L	0	0	1		
E148Q	0	7	1		

[a]Statistical difference is caused between attack-free and amyloidosis groups, [b]Data is available for 72% of the study group, [c]Participants at the control and attack-free period have a similar duration of education; but higher compared to other groups, [d]Differences were caused from amyloidosis group, [e]Other types of attack like myalgia and orchitis were not available in the study population, [e]Number of single gene mutations was counted to result, some data is missing. IQR: Interquartile range

with amyloidosis had higher levels of median proteinuria when compared to other FMF groups (p=0.036,0.001 and <0.001 in order, Table 2). But when CRP and ESR levels at attack-free were compared, all patient groups had similar CRP and sedimentation levels (p=0.942).

Discussion

In this study, we observed for the first time, plasma sTREM-1 levels were negatively correlated with the clinical activity score of FMF patients. Mean levels were not correlated with markers of ongoing inflammation. Meanwhile, sTREM-1 levels were not found elevated in FMF patients when compared to healthy controls.

Soluble TREM-1 levels were first studied in patients with FMF in 2019 by Gorlier et al.[12]. They enrolled 56 FMF patients and 6 of them had amyloidosis. Similar to our results, no significant difference was observed between patients at the attack and attack-free periods, and also correlation was not observed with CRP and ESR levels. But they showed higher levels of sTREM-1 in patients with amyloidosis even though SAA levels (SAA) were normal.[12] In another study, patients with FMF (42 with amyloidosis) and for control, 5 patients with AA amyloidosis secondary to other inflammatory diseases, and 20 healthy individuals were enrolled. Soluble TREM-1 levels were significantly higher in the FMF amyloidosis group compared to FMF without amyloidosis and healthy controls whereas levels were similar between FMF patients and healthy controls.[13] Our results were not showed any difference between patients with/without amyloidosis. Compatible with Ugurlu and Egeli[13] results, we did not show any difference between patients and healthy controls. These studies showed a significant relationship between serum levels of sTREM-1 and amyloidosis whereas our results did not align with these results. The first report in 2019, compared 6 amyloidosis patients with 50 FMF patients, and the other 42 amyloid-positive FMF patients with 20 patients without amyloidosis. Study population may affect results and there is more uniform distribution in the number of groups in our study.

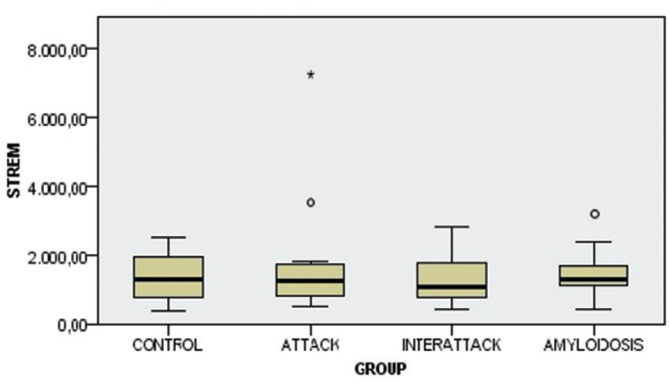

Figure 1. Independent Samples Kruskal-Wallis test

We also did not observe a significant correlation between sTREM-1, CRP, and ESR levels. In our study majority of patients were in remission and median levels of CRP and ESR were similar during the attack-free period. We suggest that fewer patients with active disease as part of our study may have an impact on this outcome. sTREM-1 levels did not increase in patients during the attack period in our study, compatible with previous results.[13] So, we can conclude that

Table 2. Clinical and laboratory features of patients

	Patient at attack period (n=16)	Patients at attack-free period (n=30)	Patients with amyloidosis (n=19)	p
Colchicine dose [mg/day, (median (IQR)]	1 (1.38)	1.25 (1)	1 (1)	0.92
Treatment				
Only colchicine	6	18	1	NA
Colchicine+IL-1 antagonists	7	10	16	
Only IL-1 antagonits	3	2	2	
AIDAI score [median (IQR)][a]	3.5 (5.25)	4 (4.5)	0 (4)	0.036
Corresponding inflammatory disease[b]				
Spondylitis [number (%)]	3	5	3	0.9
Psoriasis [number (%)]	0	0	2	
Vasculitis [number (%)]	1	1	1	
CRP [mg/L, median (IQR)][c]	10.5 (11.25)	3 (4,8)	4 (7)	**0.036**
ESR [mm/hour median (IQR)][c]	19.5 (17.5)	13 (9)	18.5 (18.25)	**0.001**
Urinary protein/creatinine excretion [mg/day median (IQR)][d]	87.5 (94)	74 (81)	1542 (1791)	**<0.001**
sTREM(pg/mL median(IQR))	1256 (940)	1076 (855)	1296 (772)	0.67

[a]Difference is caused by the attack group, [b]There were no any patients with corresponding Behcet's or Inflammatory bowel disease, [c]Difference is caused by attack group, [d]Difference is caused from amyloidosis group. AIDAI: Autoinflammatory diseases activity score, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IL-1: Interleukin 1, IQR: Interquartile range, sTREM: Serum triggering receptor expressed on myeloid cells-1

sTREM-1 levels are not a useful tool for predicting FMF attacks.

In our study age and body mass index, had a positive correlation with serum TREM-1 levels. Macrophages located in adipose tissue contribute to low-grade inflammation that causes metabolic dysfunction in obese patients. TREM-1 is also secreted by myeloid cells in adipose tissue and recently, this marker had studied in obese and normal-weight patients.[17] They showed a positive correlation between sTREM-1 levels and BMI, but not with CRP levels. Considering that data, BMI affects serum levels of sTREM-1. The relationship between age and sTREM-1 levels is controversial in previous studies. Some studies showed a correlation between age and sTREM-1 levels.[12,18,19] Minimal increased inflammatory activity is described for people at increasing ages.[20-22] So, this relationship may be related to physiological changes.

Also, we found a negative correlation between clinical activity score and sTREM-1 levels in patients with FMF. Despite the growing information about FMF pathogenesis, pyrin's mechanisms of immune system regulation remain unclear and often contradictory. IFN-γ, TNF-α, IL-6, IL-12, and IL-17 are increased in FMF even in the attack-free period, IL-4,17,22 were found to be normal in patients with FMF when compared to healthy controls.[23] In the same study, they have shown that IL-1 levels were also similar between patients and healthy controls despite the important effect of this interleukin in the pathogenesis. A negative correlation between clinical activity and sTREM-1 levels may be associated with Th1/Th2/Th17 pathway disturbances related to the predominance of innate immune system response. More studies are needed to elucidate this topic. However, the presence of markers associated with the clinical activity may be useful in clinical practice, especially for patients who are not competent to describe attack history.

sTREM-1 levels were proven to have a relation with higher disease activity in many autoimmune conditions like scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. Also, it is involved with systemic manifestations of these conditions like SLE- thrombosis, neuropsychiatric SLE, and scleroderma-pulmonary involvement.[10,24,25] Also, in autoinflammatory conditions, a recent study showed higher sTREM-1 levels in AOSD patients with higher disease activity. They also showed that sTREM-1 levels are an independent risk factor for the chronic course of AOSD.[11] The clinical course of AOSD is highly diverse and has different cytokine pathways. The systemic pattern favors the IL-1b, IL-18, and IFN-c, whereas IL-6, TNF-a, and IL-8 predominate in the chronic articular pattern.[26] Systemic involvement of AOSD mostly has an implication of autoinflammatory disease more than chronic course. The relationship between sTREM-1 and other autoinflammatory conditions has not been documented yet.

Study Limitations

This study has some limitations. Firstly, we were unable to collect SAA due to technical deficiencies in our laboratory. There is a strong relationship between SAA levels and the risk of amyloidosis.[27] Also, our study population is mostly composed of patients without ongoing inflammation and in remission period. The inclusion of inadequately treated patients can increase the reliability of the data.

Conclusion

Higher levels of sTREM-1 are associated with the clinical activity but are not predictive of attack period and amyloidosis in patients with FMF. sTREM-1 is not superior to non-specific acute phase reactants in FMF especially when patients are in an attack period.

Ethics

Ethics Committee Approval: The Local Ethical Committee of Gazi University approved the study (approval number: 622, date: 25.12.2017).

Informed Consent: Informed consent was obtained from all participants and kept in study documents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Y., H.K., Design: D.Y., H.K., Data Collection or Processing: A.A., E.E., Analysis or Interpretation: A.E., Literature Search: H.K., Writing: D.Y.

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