

Research Article

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Evaluation of Gas6 and sAxl levels during attacks and attack-free periods of familial Mediterranean fever

Ailesel Akdeniz ateşinin atak ve remisyon dönemlerinde Gas6 ve sAxl düzeylerinin değerlendirilmesi

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Abstract

Objectives: We aimed to assess the growth arrest specific protein 6 (Gas6) and soluble Axl (sAxl) levels in the familial Mediterranean fever (FMF) patients, and to investigate the correlation between the levels of these with the inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fibrinogen.

Materials and methods: Seventy nine FMF patients (35 in attack period and 44 in attack-free period) and 40 healthy controls were involved in the study. The levels of serum Gas6 and sAxl were measured by enzyme-linked immunosorbent assay (ELISA) method.

Results: Gas6 levels of the FMF patients with attack were significantly lower than both the attack-free patients and the healthy controls ($p=0.007$ and $p=0.003$, respectively). However, no significant difference was detected between the Gas6 levels of the attack-free patients and the healthy controls ($p>0.05$). sAxl levels of the FMF patients with attack were significantly lower than the healthy control ($p=0.007$). A positive correlation was found between the Gas6 and CRP levels of the FMF patients with attack ($r=0.379$, $p=0.025$).

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Conclusions: This study indicates that decreased serum Gas6 and sAxl levels may be associated with FMF attack period. Further studies on the role of the Gas6/Axl system in FMF are needed.

Keywords: Familial Mediterranean fever; Growth arrest specific 6; Tyrosine kinase receptor; Inflammation; Apoptosis.

Özet

Amaç: Bu çalışmada, Ailesel Akdeniz ateşi (AAA) hastalarında büyüme durdurucu spesifik protein 6 (Gas6) ve çözünür Axl (sAxl) düzeylerini değerlendirmeyi ve bunların C-reaktif protein (CRP), eritrosit sedimentasyon hızı (ESR) ve fibrinojen gibi inflamatuvar belirteçlerle ilişkisini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya 79 AAA'lı hasta (atak döneminde 35, remisyon döneminde 44) ve 40 sağlıklı birey dahil edildi. Serum Gas6 ve sAxl seviyeleri enzim bağılı immün assay (ELISA) yöntemi ile ölçüldü.

Bulgular: Atak döneminde olan AAA'lı hastalarda Gas6 düzeyleri hem remisyon döneminde olan hastalardan hemde sağlıklı kontrollerden anlamlı derecede düşüktü (sırasıyla, $p=0.007$ ve $p=0.003$). Bununla birlikte, remisyon döneminde olan hastalar ile sağlıklı kontroller arasında anlamlı farklılık saptanmadı ($p>0.05$). Atak döneminde olan hastalarda sAxl düzeyleri sağlıklı kontrol grubundan anlamlı derecede düşüktü ($p=0.007$). Atak döneminde olan hastalarda, Gas6 düzeyi ile CRP düzeyi arasında pozitif korelasyon bulundu ($r=0.379$, $p=0.025$).

Sonuç: Bu çalışma, azalmış serum Gas6 ve sAxl düzeylerinin AAA atak dönemi ile ilişkili olabileceğini



göstermektedir. AAA'da, Gas6/Axl sisteminin rolü üzerine daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ailesel Akdeniz ateşi; Büyüme durdurucu spesifik protein 6; Tirozin kinaz reseptör; İnflamasyon; Apoptozis.

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disease which proceeds with clinical symptoms such as fever, pleuritis, arthritis, myalgia, and erysipelas-like erythema. FMF, which shows an autosomal recessive inheritance, is commonly seen in Jewish, Armenian, Arabic and Turkish societies [1, 2]. Although it is known that a mutation in Mediterranean fever (MEFV) gene plays a crucial role in the pathogenesis of FMF, the pathologic mechanism of the disease has not been fully enlightened [3]. The MEFV gene encodes the pyrin (or marenstrin) protein which plays an important role in the regulation of the inflammation and the apoptosis [4, 5]. In FMF disease, defective pyrin protein due to mutant MEFV is responsible for the overproduction of the interleukin-1 β (IL-1 β) and the dysregulation of the apoptosis which results in uncontrolled inflammation [6]. As vitamin K-dependent growth arrest specific 6 (Gas6) protein is a ligand for the TAM receptors (Tyro3, Axl, Mer) which are the member of the receptor tyrosine kinase family, it binds to the Axl receptor with a greater affinity [7]. The interaction of Gas6 and TAM receptors protects innate immune cells against apoptosis by activating PI3K/Akt signaling pathway. Besides, Gas6 functions as a bridge molecule between TAM receptors on apoptotic and phagocytic cells. Whereas this interaction provides the initiation of the apoptotic cells' phagocytosis, it also leads to reduction in the production of the proinflammatory cytokines by inhibiting both signal transducer and activator of transcription 1 (STAT1) and nuclear factor NF- κ B signaling pathways [8, 9]. Membrane-bound Axl is present in the circulation as the soluble Axl (sAxl) form after degradation by an unknown protease. The sAxl, which is the extracellular unit of the Axl membrane protein, binds to the Gas6 in the circulation and prevents the activation of the TAM receptors by inactivating Gas6 [10, 11]. In previous studies it was reported that, Gas6/TAM system plays important role in several pathological conditions such as autoimmune, cardiovascular and systemic inflammatory diseases, and cancer [8, 12–14]. In this study, we aimed to analyze the levels of Gas and sAxl in FMF patients as well as their correlation with inflammatory markers.

Materials and methods

Seventy nine patients, diagnosed as FMF in the Department of Internal Medicine in Mustafa Kemal University, and 40 healthy people were included in the study. FMF patients were categorized as 35 patients during an attack and 44 patients in attack-free period (described as being free of attacks for at least 3 weeks). All patients were diagnosed with FMF based on the Tel-Hashomer criteria [15] and were receiving colchicine. The diagnosis of attack period was based on the presence of clinical findings, including fever, abdominal pain, arthritis, pleuritis, and skin rash and elevated acute phase reactants such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen. Laboratory findings such as complete blood count, total protein, albumin, urea, creatinine, ESR, CRP, fibrinogen, and demographic features of the subjects were recorded. Also, Gas6 and sAxl levels of the subjects in the patient and the control groups were measured. The people who have other inflammatory diseases, malignancies and infections, are pregnant, smoke, drink alcohol, and take medicines other than colchicine were not included in the study.

Specimen collection and analysis

Blood samples, collected from the patient and the control groups after an 8–12 h fasting with a serum separator tube (SST, Becton, Dickinson & Company, Franklin Lakes, NJ, USA) to measure Gas6 and sAxl levels, were centrifuged at 1500g at 4°C for 10 min. The serum parts of the blood were kept at –78°C till the experiment day. Total protein, albumin, urea and creatinine levels with Abbott Architect c8000 analyzer, CRP levels with Siemens' BNII nephelometer analyzer, ESR levels with Test-1 analyzer, fibrinogen levels with STA Compact coagulation analyzer, and complete blood count with Sysmex XN-1000 analyzer were measured with classical methods. Serum sAxl was detected using a human ELISA kit (RayBiotech, Inc.), and the inter- and intra-assay CV for sAxl were <12% and <10%, respectively. Serum Gas6 was detected using a human ELISA kit (Cusabio Inc.), and the inter- and intra-assay CV for sAxl were <10% and <8%, respectively.

Statistical analysis

For the statistical analyses, SPSS 22.0 (SPSS Inc., Chicago, IL, USA) program was used. Normality distribution of variables was analyzed with Kolmogorov-Smirnov test.

In the analysis of the quantitative data, ANOVA, Kruskal-Wallis, Mann-Whitney U-tests were used. In the analysis of the qualitative data, χ^2 test was used. Correlations were assessed using Spearman correlation test. p-Values less than 0.05 were regarded as statistically significant.

Results

The study included 35 FMF patients with attack, 44 FMF patients without attack, and 40 healthy controls. Demographic features and laboratory findings of FMF patients in attack and attack-free periods and healthy controls were summarized in Tables 1 and 2, respectively.

Regarding demographic features, no significant difference between the groups were found. ESR, CRP and

fibrinogen levels of the FMF patients in attack period were found significantly higher than the FMF patients in attack-free period. Whereas the white blood cell (WBC) count of the FMF patients in attack period were found significantly higher than both the FMF patients in attack-free period and the healthy controls, the albumin and hemoglobin levels were found significantly lower.

Gas6 and sAxl levels

Gas6 levels of the FMF patients in attack were obtained significantly lower than both the FMF patients in attack-free period and the healthy controls ($p=0.007$ and $p=0.003$, respectively). However, no significant difference was detected between the Gas6 levels of the FMF patients in attack-free period and the healthy controls ($p>0.05$; Figure 1).

Table 1: Comparison of demographic features in familial Mediterranean fever (FMF) patients and healthy controls.

	FMF (attack-free) n=44	FMF (attack) n=35	Healthy control n=40	p-Value
Age (years)	30 (18–55)	31 (16–54)	30 (18–56)	0.763 ⁱ
Gender (male), n (%)	26 (59.1)	20 (57.1)	23 (57.5)	0.982 ⁱⁱⁱ
Age at onset (years)	14 (2–47)	10 (2–51)	–	0.163 ⁱⁱ
Age at diagnosis (years)	24.3 (7–48)	22 (6–53)	–	0.759 ⁱⁱ
Delay in diagnosis (years)	6.5 (0.5–36)	9 (1–27)	–	0.172 ⁱⁱ
Disease duration (years)	12 (1–40)	19 (2–49)	–	0.133 ⁱⁱ
Colchicine dose (mg/day)	1 (0.5–2)	1.5 (0.5–2)	–	0.231 ⁱⁱ
Previous abdominal surgery, n (%)	10 (22.7)	10 (28.6)	–	0.553 ⁱⁱⁱ

ⁱKruskal-Wallis; ⁱⁱMann-Whitney U-test; ⁱⁱⁱChi square test. Data are shown as median (min–max) or number (%).

Table 2: Comparison of laboratory parameters in familial Mediterranean fever (FMF) patients and healthy controls.

	FMF (attack-free) n=44	FMF (attack) n=35	Healthy control n=40	p-Value
Urea (mg/dL)	10.7 ± 3.4	9.9 ± 3.7	11.4 ± 2.8	0.205 ⁱ
Creatinine (mg/dL)	0.71 (0.54–1.24)	0.71 (0.52–1.13)	0.74 (0.59–1.04)	0.888 ⁱⁱ
Total protein	6.9 (6.2–7.7)	6.9 (5.6–7.9)	6.8 (6.3–7.4)	0.517 ⁱⁱ
Albumin (g/dL) ^{a,b,c}	4.1 (3.7–4.9)	4 (3–4.6)	4.2 (3.8–5.3)	0.014 ⁱⁱ
WBC ($\times 10^3/\mu\text{L}$) ^{a,b,c}	7.0 (3.4–11.9)	8.1 (4.7–20.0)	6.9 (4.3–12.5)	0.003 ⁱⁱ
Hemoglobin (g/dL) ^{a,b,c}	14.9 (10.8–17.3)	13.9 (9.8–15.6)	14.7 (10.5–17.4)	0.007 ⁱⁱ
Platelets ($\times 10^3/\mu\text{L}$)	258 (153–393)	268.5 (150–627)	268 (163–522)	0.726 ⁱⁱ
Gas6 (ng/mL) ^{a,b,c}	11.9 (4.6–31.1)	9.4 (2.4–44)	13.3 (8.2–58.9)	0.004 ⁱⁱ
sAxl (pg/mL) ^{b,c}	359 (182.1–620.5)	332.9 (212.1–766.3)	413 (251.8–766.7)	0.014 ⁱⁱ
ESR (mm/h) ^a	12 (2–47)	34 (7–114)	–	<0.001 ⁱⁱⁱ
CRP (mg/L) ^a	3.3 (3.2–10.6)	49.4 (6.1–211)	–	<0.001 ⁱⁱⁱ
Fibrinogen (mg/dL) ^a	306 (183–410)	459 (278–799)	–	<0.001 ⁱⁱⁱ

ⁱANOVA; ⁱⁱKruskal-Wallis; ⁱⁱⁱMann-Whitney U-test. CRP, C-reactive protein. Data are shown as median (min–max) or mean ± standard deviation; ESR, erythrocyte sedimentation rate; WBC, white blood cell; Gas6, growth arrest-specific protein 6; sAxl, soluble forms of Axl. ^a $p < 0.05$ for FMF patients with attack vs. attack-free FMF patients. ^b $p < 0.05$ for FMF patients with attack vs. healthy controls. ^c $p > 0.05$ for attack-free FMF patients vs. healthy controls.

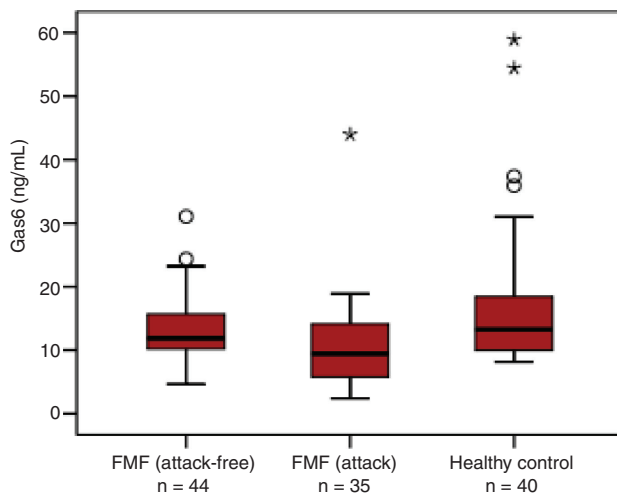


Figure 1: Serum Gas6 levels of FMF patients and controls. The Gas6 levels of the FMF patients in the attack period were found significantly lower than both in the attack-free patients and the healthy controls ($p = 0.007$ and $p = 0.003$, respectively).

sAxl levels of the FMF patients in attack period were obtained significantly lower than the healthy control group ($p = 0.007$). Levels of sAxl in attack-free FMF patients were similar to both patients with attack and healthy controls ($p > 0.05$; Figure 2).

Correlation analyses

We evaluated the correlation of the Gas6 and sAxl levels with the demographic properties and laboratory results

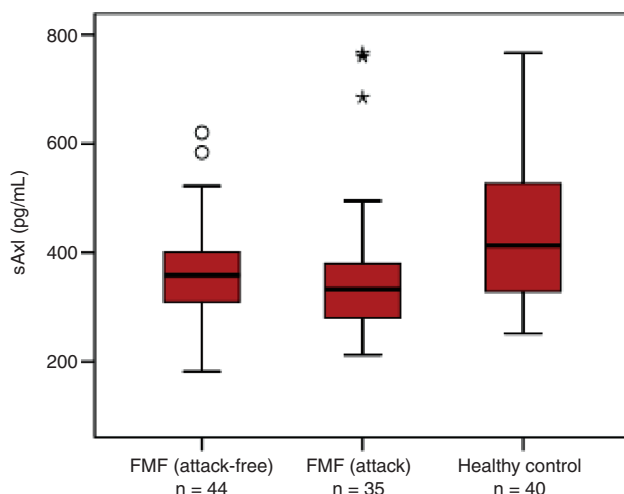


Figure 2: Serum sAxl levels of FMF patients and controls. The sAxl levels of the FMF patients in the attack periods were found significantly lower than the healthy controls ($p = 0.007$).

in all subjects, FMF patients and controls. There was no significant correlation between the Gas6 and sAxl levels with the age, disease duration, colchicine dose, urea, creatinine, total protein, albumin, WBC count, hemoglobin, platelet, ESR, CRP and fibrinogen levels ($p > 0.05$). On the other hand, a positive correlation was detected between Gas6 and sAxl levels ($r = 0.251$, $p = 0.010$).

When patients with and without FMF attack were examined as separate groups, only Gas6 levels showed positive correlation with CRP levels in FMF patients during attack ($r = 0.379$, $p = 0.025$), while no significant correlations were detected between either Gas6 or sAxl levels with the studied parameters in attack-free patients ($p > 0.05$).

Discussion

Gas6/TAM system has effective functions in adhesion, migration, survival, and proliferation of the cells, in the clearance of apoptotic cell bodies, and in the regulation of the proinflammatory cytokines' secretion [8, 9]. The alterations in the levels of the Gas6/TAM system components play important roles in the pathogenesis of many diseases such as; cancer [14], chronic renal failure [16], cardiovascular diseases [17], and rheumatic diseases [18, 19]. To our knowledge, our study is the first study investigating the Gas6 and sAxl levels in the FMF patients.

The most prominent features of the FMF disease are the massive penetration of the neutrophils into the inflammation area and possessing self-restrictive intensive inflammation periods [20]. However, the timely elimination of the neutrophils via apoptosis and the clearance of the apoptotic cells play important roles in the successful resolution of the inflammation and in the prevention of tissue damage [21, 22]. In the present study, we found the Gas6 levels of the FMF patients in attack period significantly lower than the patients in attack-free period and the healthy controls. We think that, the low Gas6 levels may contribute to inflammation and tissue damage by causing the incomplete elimination of the apoptotic cells. Moreover, Gas6-Axl system can mediate potential proinflammatory signals, and this may be an especially relevant pathway in FMF. Alciato et al. [23] suggested that the Gas6 inhibits the expression of proinflammatory cytokines such as tumor necrosis factor- α , interleukin-1 and interleukin-6 in monocytes/macrophages. Studies have shown increased proinflammatory cytokines in patients with FMF during the attack period [24, 25]. Regarding the effect of Gas6 on secretion of proinflammatory cytokine,

we speculate that high proinflammatory cytokine levels during FMF attacks may be associated with low Gas6 levels. Besides, no significant difference was found between the FMF patients in attack-free period and the healthy controls in terms of Gas6 levels. Therefore Gas6 parameter may be considered as a marker of relapse in the FMF patients.

In this study, the levels of CRP, ESR, fibrinogen and WBC, which indicate the presence and the severity of the inflammation, were obtained significantly higher in FMF patients during the attack period compared to the ones in attack-free period. In addition, there was a positive correlation between CRP and Gas6 levels of the FMF patients in attack period. Bassyouni et al. [19] found a positive correlation between the Gas6 and ESR, leukocytosis, and IL6 levels in the rheumatoid arthritis patients. In another study, Ekman et al. [26] found a positive correlation between Gas6 and, CRP and ESR levels in systemic lupus erythematosus patients. These findings suggest that Gas6 may be implicated in the systemic inflammation.

In our study, there was no correlation between sAxl and inflammatory markers including ESR, CRP, WBC and fibrinogen. In line with our finding, Ko et al. [27] observed no correlation between sAxl and, CRP and WBC levels in pneumonia patients. Notwithstanding with this, in other studies, positive correlations were reported between the sAxl level and inflammatory markers such as ESR, CRP, tumor necrosis factor-alpha and interleukin-6 [26, 28]. These results demonstrate that the interaction between sAxl and inflammatory markers in various diseases is contradictory. The reason of this discrepancy may arise from the interaction of Gas6 with the other receptors of tyrosine kinases apart from Axl and also the unique characteristics of the populations included in these studies.

In conclusion, sAxl levels of the FMF patients with attack were found significantly lower than the healthy controls. Gas6 levels of the FMF patients in the attack period were significantly lower than FMF patients in the attack-free period and healthy controls. Gas6 levels were positively correlated with CRP in the FMF patients with attack. However, further investigations are required to understand the potential role of Gas6/Axl system and to help in the development of diagnosis and treatment strategies of FMF.

This study had several limitations. First of all, this is a cross-sectional study of Gas6 and sAxl levels in attack and attack-free periods of FMF. The parameters should also be assessed during the attack and attack-free periods of the same patients. Secondly, a control group with disease is also required to record shifts specific for FMF. Thirdly, this study was carried out at a single center and with a

small sample size. Fourthly, all TAM receptor tyrosine kinases and proinflammatory cytokines have not been investigated.

Ethical aspects: The institutional ethics committee of the Mustafa Kemal University has approved the protocol of this study. [The protocol code for this study: 20/01/2016/34.]

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Conflict of interest statement: The authors state no conflict of interest.

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