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The Relation Between Serum Alpha Defensin-1 Levels with Clinical Course and Prognosis in Crimean-Congo Hemorrhagic Fever

Kırım-Kongo Kanamalı Ateşinde Serum Alfa Defensin-1 Düzeylerinin Klinik Seyir ve Prognoz ile İlişkisi

Meral BAYAR[1]
0000-0001-7391-5533
Emine PARLAK[2]
0000-0001-8912-6360
Esra LALOĞLU[3]
0000-0001-5189-3564
Mehmet PARLAK[2]
0000-0002-6235-4862
Sinan YILMAZ[4]
0000-0001-7784-3274

[1]Department of Infectious Diseases and Clinical Microbiology, Çanakkale Ezine State Hospital, Çanakkale, Turkey

[2]Department of Infectious Diseases and Clinical Microbiology, Atatürk University Faculty of Medicine, Erzurum, Turkey

[3]Department of Medical Biochemistry, Atatürk University Faculty of Medicine, Erzurum, Turkey

[4]Department of Public Health, Atatürk University Faculty of Medicine, Erzurum, Turkey

Corresponding Author
Sorumlu Yazar
Esra LALOĞLU
esra.laloglu@atauni.edu.tr

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ABSTRACT

Aim: Crimean-Congo Hemorrhagic Fever (CCHF) is a viral zoonotic infection characterized by fever and bleeding. Alpha-defensin-1 (AD-1) is an antimicrobial peptide. The aim of this study was to investigate the relationship between the clinical course and prognosis of CCHF and AD-1 serum levels, and also to examine the role of AD-1 in the pathogenesis of the disease.
Material and Methods: Fifty patients diagnosed with CCHF and hospitalized at the Atatürk University Faculty of Medicine Department of Infectious Diseases and Clinical Microbiology, and 38 healthy control were included in this study. Serum AD-1 levels were measured using ELISA methods and compared between the groups.
Results: Serum AD-1 levels in the patients were significantly higher than those in the control group (p=0.017). Of the patients, 18 (36%) were classified as severe clinical course, 16 (32%) as moderate clinical course, and 16 (32%) as mild clinical course. There was no statistically significant difference among the three groups in terms of serum AD-1 levels (p=0.729). Median serum AD-1 levels were 171.0 (range, 126.8-221.2) ng/ml in the fatal cases, and 118.7 (range, 91.9-183.3) ng/ml in the surviving patients, and the difference between these two groups was statistically significant (p=0.014).
Conclusion: As a result, the increased serum AD-1 levels in CCHF patients, remained higher in severe course patients and in the fatal cases. On the basis of these results, AD-1 appears to indicate the clinical course and provide useful information about mortality. More extensive research should be performed to make generalizations on this subject.
Keywords: Alpha defensin-1; antimicrobial peptide; Crimean-Congo Hemorrhagic Fever.

ÖZ

Amaç: Kırım-Kongo Kanamalı Ateşi (KKKA), ateş ve kanama ile seyreden zoonotik viral bir enfeksiyondur. Alfa defensin-1 (AD-1) antimikrobiyal bir proteindir. Bu çalışmanın amacı AD-1 düzeyleri ile KKKA'da klinik seyir ve prognoz arasındaki ilişkiyi araştırmak, aynı zamanda AD-1'in hastalığın patogenezindeki rolünü de incelemektir.
Gereç ve Yöntemler: Bu çalışmaya KKKA tanısı almış olan ve Atatürk Üniversitesi Tıp Fakültesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümünde yatarak takip edilen 50 hasta ve 38 sağlıklı kontrol dahil edildi. Serum AD-1 düzeyleri ELISA yöntemi ile ölçüldü ve gruplar arasında karşılaştırıldı.
Bulgular: Hastalardaki serum AD-1 düzeyleri kontrol grubundan anlamlı şekilde daha yüksekti (p=0,017). Hastaların 18 (%36)'i ağır klinik seyir, 16 (%32)'sı orta düzeyde klinik seyir ve 16 (%32)'sı hafif klinik seyir olarak sınıflandırıldı. Serum AD-1 düzeyleri açısından bu üç grup arasında istatistiksel olarak anlamlı bir farklılık yoktu (p=0,729). Ortanca serum AD-1 seviyeleri, ölümcül vakalarda 171,0 (aralık, 126,8-221,2) ng/ml ve hayatta kalan hastalarda 118,7 (aralık, 91,9-183,3) ng/ml idi ve bu iki grup arasındaki bu farklılık istatistiksel olarak anlamlı idi (p=0,014).
Sonuç: Sonuç olarak, KKKA hastalarında artan serum AD-1 düzeyleri ağır seyirli hastalarda ve ölümcül vakalarda daha da yüksek seyretmektedir. Bu sonuçlara dayalı olarak, AD-1'in klinik seyri gösterdiği ve mortalite hakkında faydalı bilgiler sağladığı görülmektedir. Bu konuda genellemeler yapabilmek için daha geniş çaplı araştırmalar yapılmalıdır.
Anahtar kelimeler: Alfa defensin-1; antimikrobiyal peptidler; Kırım-Kongo Kanamalı Ateşi.

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INTRODUCTION

The agent involved in Crimean-Congo Hemorrhagic Fever (CCHF) is an enveloped RNA virus belonging to the *orthonairovirus* genus from the family *Nairoviridae* (1). The virus is particularly borne by *Hyalomma marginatum marginatum* ticks. The infection is transmitted due to infected ticks adhering to humans, nosocomial transmission, and through body fluids such as blood from animals in the viremic period. The infection has a high mortality. CCHF is the most common viral hemorrhagic fever worldwide. The incubation period is 3-7 days. Initial symptoms are characterized by sudden onset fever, headache, muscle pain, and dizziness. Hemorrhage is most commonly seen from the nose and gums, while hematemesis, melena, hematuria, hemoptysis, and intra-abdominal and vaginal bleeding may also be seen in patients with a clinically severe course (2,3).

The defensins, which are arginine-rich molecules, are the most important antimicrobial peptide group in mammals (4). They consist of 30-40 amino acids with molecular weights between an average of 3 and 6 kDa (5). The defensins are expressed by monocyte/macrophages, some T lymphocyte cells, immature dendritic cells, and natural killer (NK) cells in humans (6).

Defensins are closely related to protein-protein and protein-DNA interactions. This interaction contributes to binding to enveloped and non-enveloped (HPV and human adenovirus, HAdV) viruses. Since defensins are cationic and amphipathic, they can react in a charge-charge manner with ligands and also hydrophobically. For α-defensin in particular, defensin oligomerization and structural stability deriving from the disulfide bond may have a greater effect on binding (7).

Enveloped viruses have to create a fusion between the lipid bilayer and the host cell membrane, in order to introduce their own genes into the host cell. Alpha defensin-1 (AD-1) binding thus directly alters HIV-1 fusion through the interaction with gp 41. AD 1-4 directly prevents binding and adhesion to HIV-1 (8). Defensins' ability to serve as lectin and their selective sugar-binding capacities contribute to their antiviral properties (7). AD 1-3 have been shown to be effective against HIV, to whose receptors they bind with high affinity with their lectin-like properties (9).

The pathogenesis of CCHF is not fully understood. The immune system is important, but the response is insufficient in patients with severe disease. Defensin production begins as a result of viral infections. Defensins are known to be able to play direct and indirect roles in viral pathogenesis. Studies have investigated AD-1 levels in some viral diseases, but none have yet been considered AD-1 in CCHF. The purpose of this study was to determine AD-1 levels in patients with CCHF and to evaluate its relationship with clinical severity.

MATERIAL AND METHODS

Patients

Fifty patients definitively diagnosed with CCHF through investigation of samples using RT-PCR and/or ELISA and hospitalized for monitoring at the Atatürk University Infectious Diseases and Clinical Microbiology Clinical were included in the study. The study protocol was approved by the local ethics committee (24.05.2012, 21-5), and written informed consent was obtained from all patients included in the study. The study was designed and conducted in accordance with the ethical guidelines in the Declaration of Helsinki. Patients were divided into mild/moderate and severe on the basis of clinical severity. The defined criteria for patients were the presence of at least one; leukocyte count ≥10,000/mm^3, thrombocyte count ≤20,000/mm^3, aspartate aminotransferase (AST) ≥200 IU/L, alanine aminotransferase (ALT) ≥150 IU/L, activated partial thromboplastin time (aPTT) ≥60 sec, or fibrinogen ≤110 µg/dl in the first 5 days after onset of clinical symptoms as a severe case and absence of any of these as a mild/moderate case (10). Thirty-eight healthy volunteers were enrolled as the control group.

Biochemical Evaluation

Patient blood specimens were collected on a voluntary basis. Written informed consent was obtained from all patients before the examination. Five-milliliter blood specimens were collected after hospitalization. After 30 min these were then centrifuged for 5 min at 2000 rpm for sera separation. One milliliter was placed into one Eppendorf tube and 2 ml into another one. Two mL serum samples were sent to the Refik Saydam Hygiene Center reference laboratory in accordance with the appropriate transportation norms. Patients included in this study were those identified with specific IgM antibody positivity as a result of tests performed by that reference laboratory or with the presence of CCHF virus in sera confirmed using PCR. Thirty-eight healthy individuals were enrolled as a control group. Patient and control group sera (in 1 ml tubes) were stored at -80 °C until the study.

Serum AST, ALT, creatine phosphokinase (CK), lactate dehydrogenase (LDH) levels were measured using original kits on a Roche Diagnostics device (Roche Diagnostics, Mannheim, Germany), while hemogram parameters as white blood cell (WBC) and platelet (PLT) were determined with the Beckman Coulter LH 780 (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland) device in the laboratory. Prothrombin time (PT-INR) and aPTT were analyzed in the ACL Top 700 ® (Instrumentation Laboratory, Bedford, MA, USA).

Serum AD-1 Level Measurement

Serum AD-1 levels were measured using a commercial ELISA kit (USCN, P.R. China) (SEB705Hu for Defensin Alpha 1, Neutrophil DEF a1, Human). In line with the test procedure, 100 µL of serum sample was added to each ELISA plaque well and was then incubated for 2 h at 37 ºC. The wells were then emptied and 100 µL of previously prepared detection reagent A was placed in each well and incubated for 1 h at 37 ºC. The wells were then emptied and washed three times. Next, 100 µL detection reagent B was placed in the wells and incubated for 30 min at 37 ºC. The wells were then emptied and washed five times; 90 µL substrate solution was then added and incubated at 37 ºC for 15-20 min. Finally, a 50 µL stop solution was added with no emptying and washing and the results were expressed with 450 nanometric absorbance values. The linear range of the test was measured as 0.312-20 ng/ml.

Statistical Analysis

Statistical Package for Social Sciences (IBM-SPSS v.20.0) software was used for statistical analysis. Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Numerical data were expressed as mean and standard

deviation or median, interquartile range, minimum, and maximum values, while categorical data were expressed as numbers and percentages. The Mann-Whitney U test and Kruskal-Wallis test were used for data analysis. Relationships between results were evaluated using Spearman correlation analysis. A p value of <0.05 was regarded as significant for all tests.

RESULTS

The study group involved 50 patients, 26 (52%) male, and 24 (48%) female. The healthy control group consisted of 38 individuals, 20 male (52.6%) and 18 female (47.4%). Gender distributions in the patient group (p=0.883) and in the control group (p=0.872) were similar. The mean age of patients was 49.12±18.33 years, compared to 40.92±16.51 in the control group.

Laboratory values of patients were shown in Table 1. Mean AD-1 levels were 126.0±30.5 ng/ml in the patient group and 112.2±24.5 ng/ml in the control group, the difference being statistically significant (p=0.017).

In terms of patients' clinical courses, 18 (36%) were classified as severe, 16 (32%) as moderate, and 16 (32%) as mild. Four (8%) of the 50 patients enrolled in the study died, while 46 (92%) were discharged in a healthy condition.

Serum AD-1 levels were compared among the patients with CCHF according to their clinical severity. Median AD-1 levels were 116.8 (range, 91.9-191.2) ng/ml in the mild group, 124.7 (range, 94.9-177.7) ng/ml in the moderate group, and 123.4 (range, 97.6-221.2) ng/ml in the severe group (Table 2, Figure 1). No statistically significant difference was determined among the three groups in terms of serum AD-1 levels (p=0.729). Also, AD-1 levels were significantly higher in the non-surviving patients compared to those that survived (p=0.014). The surviving patient group and the control group were compared separately in terms of AD-1 levels, the difference being threshold significant (p=0.015, Table 3).

The correlation coefficient between serum AD-1 levels and laboratory tests frequently employed in the diagnosis, treatment, and prognosis of CCHF are shown in Table 4. However, no significant correlation was determined between AD-1 level with hematological and biochemical parameters.

Table 1. Patients' non-specific laboratory findings (n=50)

Parameter	Median (Q_1-Q_3) [Min-Max]	Reference interval
WBC ($10^3/\mu$)	2 (1.5-2.6) [0.9-11.7]	4.3-10.3
PLT ($10^3/\mu L$)	36 (19-54.8) [6-128]	150-450
AST (U/L)	343 (149-521) [48-11150]	1-50
ALT (U/L)	163 (83-336) [26-2944]	1-50
CK (U/L)	634 (168-1506) [48-7641]	1-171
LDH (U/L)	636 (424-994) [186-9458]	1-247
PT (sec)	11 (10-12) [9.0-18.9]	10.0-15.9
aPTT (sec)	37 (31-40) [23-64]	26.5-36
INR	1 (0.9-1.3) [0.8-94.0]	0.9-1.3

Q_1-Q_3: 25th-75th percentile, WBC: white blood cell, PLT: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: creatine kinase, LDH: lactate dehydrogenase, PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio

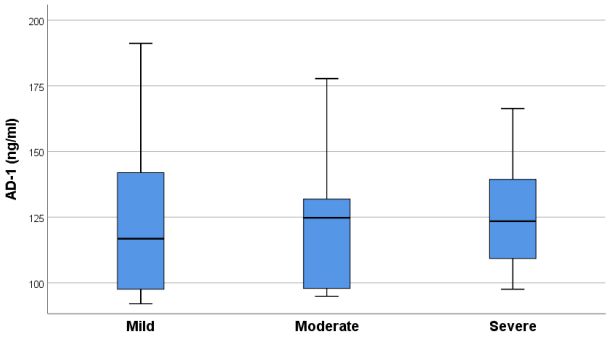

Figure 1. Demonstration of serum AD-1 levels in groups divided by severity of CCHF disease

Table 2. Disease severity and serum AD-1 levels

	Mild (n=16)	Moderate (n=16)	Severe (n=18)	p
AD-1 (ng/mL)	116.8 (97.5-142.4) [91.9-191.2]	124.7 (97.8-131.9) [94.9-177.7]	123.4 (108.0-140.6) [97.6-221.2]	0.729

AD: alpha defensin, data were expressed as median (25th - 75th percentile) [minimum-maximum]

Table 3. Comparison of AD-1 levels between surviving and non-surviving patients and the control group

	Patients (n=50)		p*	Control Group (n=38)	p#
	Surviving (n=46)	Non-surviving (n=4)			
AD-1 (ng/mL)	118.7 (98.2-133.5) [91.9-183.3]	171.0 (132.8-213.7) [126.8-221.2]	**0.014**	110.2 (92.7-129.5) [65.7-178.2]	**0.015**

AD: alpha defensin, p*: non-surviving vs. surviving patients, p#: surviving patients vs. control group, data were expressed as median (25th - 75th percentile) [minimum-maximum]

Table 4. Correlation between serum AD-1 levels and laboratory parameters

		WBC	PLT	AST	ALT	LDH	PT	aPTT	INR
AD-1 (ng/mL)	r_s	0.253	-0.027	0.063	0.116	0.029	-0.313	0.084	-0.112
	p	0.077	0.850	0.664	0.421	0.842	0.001	0.564	0.437

AD: alpha defensin, WBC: white blood cell, PLT: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, PT: prothrombin time, aPTT: activated partial thromboplastin time, INR: international normalized ratio

DISCUSSION

The principal findings of this prospective study were as follows; i) the CCHF patients exhibited higher AD-1 levels than the control group; ii) AD-1 levels were higher in fatal cases than in surviving patients; iii) WBC and PLT as the routine laboratory tests were lower in the patient group, while AST, ALT, LDH, and CK increased. Finally, AD-1 level exhibited a significant relation with clinical severity in CCHF patients. The study findings emphasize the role of AD-1 in demonstrating clinical course and prognosis in CCHF. There are no studies in the literature concerning serum AD-1 in viral hemorrhagic fevers.

The most abundant cationic peptides, an important component of the immune system with antimicrobial effects, are the defensins. These are able to inactivate several bacteria, protozoa, and viruses. They are also chemotactic agents for macrophages, T cells, and immature dendritic cells (9).

AD-1 has proven efficacy against bacteria such as *Staphylococcus aureus*, *Enterobacter aerogenes*, *Escherichia coli*, *Mycobacterium avium*, and *Mycobacterium intracellulare*. AD 1-3 have been reported to be effective against *Mycobacterium tuberculosis* (6). AD 1-3 have also been shown to inhibit enzymatic activity by binding with high affinity to anthrax lethal factor.

Direct interaction of defensins with the lipid double layer of enveloped viruses can destroy or destabilize the virus (7). They can inhibit the majority of enveloped viruses through neutralization of the lipid double membrane. The sensitivity of enveloped viruses to α-defensins varies (7). Studies investigating defensin levels in various viral diseases have confirmed their antiviral effects. AD-1 has been reported to inhibit viral replication and viral proteins in cell cultures. AD 1-4 have been shown to be effective against HSV1, HSV2, influenza virus, adenovirus, and CMV (6,11,12). AD-1 has been proved to bind directly to HSV-1 and to membranes containing phosphatidylcholine (7). Another study showed that AD 1-6 inhibited HSV infection for protection against HSV infection (9). Generally, the defensins block the host cell receptor and binding to viral glycoproteins, so they prevent HSV-1 and HSV-2 infection (13). Buck et al. (14) described AD 1-3 and AD-5 as powerful antagonists against papillomavirus infection, a non-enveloped virus. Also, other studies have shown that ADs are necessary for preventing HAV, HIV-1, HSV-1, and influenza A virus (7,8,12,14-16).

These studies support the idea that AD-1 stimulation is not specific to CCHF. The natural immune system is important in the resolution of the disease in CCHF. Inflammatory mediators play an important role in patients that die due to CCHF. Four (8%) of the 50 patients in this study died. Our study suggests that CCHF increases the release of serum AD-1 and supports previous studies. We think that the increasing AD-1 levels we identified in CCHF may contribute to host defense. This may suggest that patients dying due to CCHF have insufficient activity or levels for eradication. AD may be less sensitive in some viral strains or in a high viral load.

Defensins also are important molecules in the generation of immune response with their immunomodulatory peptide properties. They act as regulators in some diseases as a response to various inflammatory stimuli. α-defensins have recently been reported to be involved in the pathogenesis of autoimmune diseases. In a study of patients with Behçet's disease, Mumcu et al. (17) determined significantly higher AD 1-3 levels in patients with severe disease. Serum AD-1 levels were significantly higher in the fatal cases and the surviving patients in our study. So, we think that AD-1 can be used as an immunomodulator, particularly in severe and mortal patients in which viremia is high.

Defensins are known to serve as tumor cell regulators. Gunes et al. (18) reported statistically significantly high AD 1-3 in patients with bladder cancer. A correlation has been determined between AD 1-3 expression and colorectal adenoma and carcinoma (6). CCHF is also a lymphovascular disease. The virus is first replicated in the lymph glands and produces characteristic endothelial infection. AD-1 levels were high in our patients through a similar mechanism.

Alpha defensins facilitate thromboembolic events in chronic heart failure and pro-thrombosis. They increase coagulation by inhibiting tissue plasminogen activators. The relation between α-defensin and mortality has also been investigated in these patients and has been described as prognostic (19). In CCHF, a plasminogen activator inhibitor is released for the inhibition of fibrinolysis with IL-1 and TNF, and coagulation mechanisms are activated. AD-1 levels in patients with the severe and mortal diseases may have facilitated coagulation cascade activation and progression toward disseminated intravascular coagulation. It exhibited no antiviral effectiveness in these patients.

There are a number of limitations to this study. These include the fact that α-defensin only was investigated. In addition, the effect of the viral load and gene polymorphism were not investigated. Finally, we did not examine the entire cascade.

CONCLUSION

AD-1 levels increasing with the severity of the disease also play an important role in the pathogenesis of the CCHF. Higher AD-1 levels have been measured in mortal patients and those with a clinically severe course. Future studies on this subject can help illuminate the pathogenesis of CCHF infection and even direct treatment. Defensins can be used in the future in the prevention and treatment of infectious diseases. Studies with wider case series and different gene polymorphism regions are needed to shed light on treatment.

Ethics Committee Approval: The study was approved by the Non-Drug Clinical Research Ethics Committee of Atatürk University (24.05.2012, 21-5).

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