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Investigation of the Relationship Between TAFI Plasma Levels and Hemorrhage in Patients with Crimean-Congo Hemorrhagic Fever and the Role of TAFI in the Disease Pathogenesis

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Abstract

Objective: Crimean-Congo hemorrhagic fever is a tick-borne viral infection presenting with fever and bleeding. Thrombin-activatable fibrinolysis inhibitor is a plasma procarboxypeptidase synthesized in the liver, causing downregulation of fibrinolysis. The association of thrombin-activatable fibrinolysis inhibitor levels with the clinical course and pathogenesis of Crimean-Congo hemorrhagic fever has not been adequately studied. The aim of the current study was to determine plasma thrombin-activatable fibrinolysis inhibitor levels in patients with Crimean-Congo hemorrhagic fever, and to reveal its role in the clinical course of the disease and in the pathogenesis of hemorrhage.

Methods: Forty-four patients diagnosed with Crimean-Congo hemorrhagic fever and 44 control subjects were included in the study. The diagnosis of Crimean-Congo hemorrhagic fever was based on a positive result for IgM antibodies or Crimean-Congo hemorrhagic fever virus detected by PCR. The thrombin-activatable fibrinolysis inhibitor levels were analyzed.

Results: The mean age and sex distribution were similar between the groups. The white blood cell, prothrombin time, activated partial thromboplastin time, and international normalized ratio values were also comparable ($P > .05$). The mean plasma thrombin-activatable fibrinolysis inhibitor value was 429.33 ± 328.224 ng/mL in the Crimean-Congo hemorrhagic fever group, and 922.44 ± 1236.449 ng/mL for the control group ($P = .045$).

Conclusion: Reduced thrombin-activatable fibrinolysis inhibitor levels were found in Crimean-Congo hemorrhagic fever patients. Decreased thrombin-activatable fibrinolysis inhibitor levels may contribute to the impairment of the coagulation mechanism. In other words, thrombin-activatable fibrinolysis inhibitor may be involved in the pathogenesis of bleeding in Crimean-Congo hemorrhagic fever.

Keywords: Coagulation, Crimean-Congo hemorrhagic fever, fibrinolysis, polymerase chain reaction, thrombin-activatable fibrinolysis inhibitor

Kırım Kongo Kanamalı Ateşi Olan Hastalarda TAFI Plazma Düzeyleri ile Hemoraji Arasındaki İlişkinin Araştırılması ve TAFİ'nin Patogenezindeki Rolü

Öz

Amaç: Kırım-Kongo Kanamalı Ateşi, ateş ve kanama ile seyreden kene kaynaklı viral bir enfeksiyondur. Trombinle aktive olabilen fibrinoliz inhibitörü, karaciğerde sentezlenen ve fibrinolizin aşağı yönlü regülasyonuna neden olan bir plazma prokarboksipeptidazdır. trombinle aktive olabilen fibrinoliz inhibitörü düzeylerinin klinik seyir ve Kırım-Kongo Kanamalı Ateşi patogenezi ile ilişkisi yeterince araştırılmamıştır. Bu çalışmanın amacı, Kırım-Kongo Kanamalı Ateşli hastalarda plazma trombinle aktive olabilen fibrinoliz inhibitörü düzeylerini belirlemek ve hastalığın klinik seyri ve kanamanın patogenezindeki rolünü ortaya koymaktır.

Yöntemler: Çalışmaya Kırım-Kongo Kanamalı Ateşi tanısı alan 44 hasta ve 44 kontrol alındı. Kırım-Kongo Kanamalı Ateşi tanısı, pozitif IgM antikorlarına veya PCR ile tespit edilen Kırım-Kongo Kanamalı Ateşi virüsüne dayanıyordu. trombinle aktive olabilen fibrinoliz inhibitörü seviyeleri analiz edildi.

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Bulgular: Gruplar arasında ortalama yaş ve cinsiyet dağılımı benzerdi. Beyaz kan hücresi, protrombin zamanı, aktive parsiyel tromboplastin zamanı, uluslararası normalleştirilmiş oran değerleri de benzerdi ($P > ,05$). Kırım-Kongo Kanamalı Ateşi grubunda ortalama plazma trombinle aktive olabilen fibrinoliz inhibitörü değeri 429,33 ± 328,224 ng/mL, kontrol grubununki ise 922,44 ± 1236,449 ng/ml idi ($P = ,045$).

Sonuç: Kırım-Kongo Kanamalı Ateşi hastalarında azalmış trombinle aktive olabilen fibrinoliz inhibitörü seviyeleri bulundu. Azalan trombinle aktive olabilen fibrinoliz inhibitörü seviyeleri, pıhtılaşma mekanizmasının bozulmasına katkıda bulunabilir. Başka bir deyişle, trombinle aktive olabilen fibrinoliz inhibitörü, Kırım-Kongo Kanamalı Ateşi'nde kanamanın patogenezinde rol oynayabilir.

Anahtar Kelimeler: Pıhtılaşma, Kırım-Kongo Kanamalı Ateşi, fibrinoliz, polimeraz zincir reaksiyonu, trombinle aktive olan fibrinoliz inhibitörü

Viral hemorrhagic fevers progress with acute systemic fever and hemorrhage caused by various viruses. The first viral hemorrhagic fever detected in Turkey was the Crimean-Congo hemorrhagic fever (CCHF). The tick-borne virus, which is the cause of CCHF, belongs to the *Nairovirus* genus of the Bunyaviridae RNA virus family.[1] Although the pathogenesis of viral hemorrhagic fevers varies, findings such as endothelial damage and impaired hemostasis are common.[2] A sudden onset of fever, headache, weakness, anorexia, generalized pain in the body, nausea, and abdominal pain are the most common symptoms. Bleeding can range from petechiae to large hematomas in the mucosa and skin.[3]

Inflammatory mediators have an important role in fatal cases. Increased levels of cytokines (interleukin-6 (IL-6), IL-12, IL-10, and tumor necrosis factor-alpha (TNF-α)) were detected in patients who died from CCHF.[4]

The role of thrombin-activatable fibrinolysis inhibitor (TAFI) in the delicate balance between coagulation and fibrinolysis is important.[5] TAFI is a proenzyme-like plasma procarboxypeptidase produced in the liver. Upon activation by trypsin, thrombomodulin, plasmin, and thrombin, TAFI is converted to an active carboxypeptidase enzyme.[6] Activated TAFI disrupts fibrinolysis by preventing the binding of plasminogen to lysine residues at the C-terminal of fibrin fragments. Thus, TAFI is considered to stabilize the fibrin clot. Increased TAFI level is a risk factor for venous thromboembolism.[7,8]

Methods

Study population

This study was performed on patients with a diagnosis of CCHF confirmed by RT-PCR and/or ELISA testing between March 2013 and July 2014. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ataturk University Clinical Research Ethics Committee (2014/7-106). İn the study, 44 patients with CCHF and 44 control subjects were included. The patients were informed about the procedures after a detailed physical examination. Patients with chronic liver disease, chronic renal failure, diabetes mellitus, active or chronic tuberculosis, acute infection other than CCHF, pregnant women, and patients with anti-inflammatory drug use in the last 1 month or negative laboratory tests for CCHF were excluded.

Laboratory analyses

For laboratory analyses, 2 blood samples of at least 2 mL each (serum and plasma) were collected from each patient with suspected CCHF. The blood samples were stored for 30 minutes and centrifuged at 4000 rpm for 5 minutes. The sera were separated, transferred into Eppendorf tubes, and sent to the CCHF National Reference Laboratory (Refik Saydam National Public Health Agency, Ankara) for serological and virological tests for the diagnosis of CCHF. Patients who tested positive for the CCHF virus-specific IgM antibody or with the CCHF virus detected in their serum by PCR were included in the study. TAFI samples stored at −80°C were analyzed using the ELISA method, according to procedure.

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences Version 20.0 (IBM Corp, Armonk, NY, USA) software package. The results were summarized as number, percentage, mean, and standard deviation. The normality of data distribution was checked using the Kolmogorov–Smirnov test. The Student's *t*-test, Mann–Whitney *U*-test, and chi-square test were used for comparison between the groups. A value of $P < .05$ was considered significant.

Results

The study included a total of 44 patients, of whom 27 (61.4%) were male and 17 (38.6%) were female. The control group consisted of an equal number of individuals. There were 20 males (45.5%) and 24 females (54.5%) in the control group. The mean age and sex distribution were similar between the groups. The WBC (white blood cell), PT (prothrombin time), APTT (activated partial thromboplastin time), and INR (international normalized ratio) values were also comparable between the groups. TAFI and platelet count were significantly reduced, whereas AST (aspartate aminotransferase), ALT (alanine aminotransferase), CPK (creatine phosphokinase), and LDH (lactate

Table 1. Study population characteristics

	CCHF	Control	*P*
Age, years	50.48 ± 16.85	50.88 ± 14.85	.666
Sex, male, *n* (%)	27 (61.4)	20 (44.5)	.072
TAFI (ng/mL)	439 ± 328	922 ± 1236	.045*
WBC (×10³/μL)	2250 ± 777 (1700-2800)	2195 ± 1419 (300-9000)	.734
PLT (×10³/μL)	13 500 ± 6363 (9000-18 000)	31 904 ± 20 975 (8000-78 000)	<.001*
PLT (×10³/μL)	13 500 ± 6363 (9000-18 000)	31 904 ± 20 975 (8000-78 000)	<.001*
AST (IU/L)	6264 ± 2595 (4429-8100)	713 ± 855 (68-5269)	<.001*
ALT (IU/L)	3529 ± 3210 (1259-5800)	275 ± 199 (57-1046)	<.001*
CPK (IU/L)	5672 ± 2584 (3845-7500)	1014 ± 843 (162-3600)	<.001*
LDH (U/L)	9974 ± 3288 (7649-12300)	1214 ± 1300 (265-8400)	<.001*
PT (seconds)	13 ± 1.5 (12-14)	12.7 ± 3.4 (9.8-28)	.454
PTT (seconds)	75 ± 36 (51-100)	38.8 ± 11.7 (28-100)	.112
INR	1.15 ± 0.2 (1-1.3)	1.1 ± 0.32 (0.5-2.3)	.889

*$P < .05$.
Abbreviations: ALT, alanine amino transferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CCHF, Crimean-Congo hemorrhagic fever; CPK, creatine phosphokinase; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PLT, platelet; TAFI, thrombin-activatable fibrinolysis inhibitor; WBC, white blood cell.

dehydrogenase) levels were significantly increased in the CCHF group ($P < .05$) (Table 1).

The demographic characteristics of CCHF patients are shown in Table 2. Among CCHF patients, 27 (61.4%) had a history of tick bite. Of the remaining 17 patients, there was no history of tick bite in 8 (18.2%) patients. Nine (20.5%) patients had a history of contact with an infected human. The average incubation period was 3.31 days (1-9 days) in patients with known history of tick bite and 4.56 days (1-7 days) for those infected through human-to-human transmission. Blood samples were taken from 1 to 3 days after the onset of symptoms from 27 (61.36%) patients and 4-7 days later from 17 (38.63%) patients. Thirty-five patients lived in a rural area or had traveled to a rural area. While 13 patients were farmers, 12 patients were engaged in animal husbandry. The occupations of the remaining patients are summarized in Table 2.

Table 2. Demographic characteristics of CCHF patients

Demographic Characteristics	*n* (%)
History of Tick Bite	
Yes	27(61.4)
No	17(38.6)
Occupation	
Farmer	13 (29.5)
Stockbreeding	12 (27.1)
Housewife	7 (15.9)
Healthcare Worker	6 (13.6)
Other occupation	5 (11.36)
Student	1 (2.27)
Average Incubation Time (days)	3.31(1-9)

Abbreviations: CCHF, Crimean-Congo hemorrhagic fever.

In CCHF patients, the most common symptoms were fatigue (97.72%), fever (86.4%), and anorexia (81.8%). Eleven patients (25%) experienced bleeding during their hospitalization or post-discharge, with gingival bleeding and epistaxis being the most common type of hemorrhage. Vaginal bleeding and abdominal hematoma occurred in 1 patient each, and 2 patients had a hematoma in the arm. All symptoms are listed in Table 3.

The most common physical examination findings were hepatomegaly (88.6%), splenomegaly (81.8%), facial hyperemia (79.5), conjunctival hyperemia, and

Table 3. Symptoms of patients with CCHF

Symptom	*n*	%
Weakness	43	97.72
Fever	38	86.4
Anorexia	36	81.8
Generalized body pain	34	77.3
Nausea	33	75
Skin rash	27	61.4
Headache	22	50
Vomiting	17	38.6
Diarrhea	15	34.1
Abdominal pain	14	31.4
Bleeding	11	25
Cough	8	18.2
Change in consciousness	3	6.8

Abbreviations: CCHF, Crimean-Congo hemorrhagic fever.

maculopapular rash (61.4%). Bradycardia and atrial fibrillation developed in 2 patients (Table 4).

In our study, thrombocytopenia occurred in all patients and severe thrombocytopenia developed at an early stage. In 26 patients, the platelet count fell below 20 000 µL, and blood products were given. Ribavirin treatment was initiated early in all patients who were given blood products. None of the patients experienced side effects during hospitalization.

Table 4. Physical examination findings of patients with CCHF

Findings	*n*	%
Hepatomegaly	39	88.6
Splenomegaly	36	81.8
Facial hyperemia	35	79.5
Conjunctival hyperemia	27	61.4
Maculopapular rash	27	61.4
Lung auscultation finding **	13	29.5
Herpes labialis	7	15.9
Petechiae, purpura, ecchymosis	3	6.81
Bradycardia	1	2.3

*Gingival bleeding, nosebleed, vaginal bleeding.
**Rales, rhonchus, wheezing.

Discussion

The TAFI levels were significantly decreased in CCHF patients in our study.

The major at-risk groups for CCHF include farmworkers, shepherds, livestock and slaughterhouse workers, veterinarians, people in contact with sick animals and ticks, soldiers, campers, and healthcare staff. In a study including 123 CCHF cases, the predisposing factors were a history of tick bite, contact with infected animal blood, and direct exposure.[9] In our study, the rates of contact history and occupation distribution were consistent with epidemiological characteristics of other regions in the country.

Endothelial damage is the most important stage in pathogenesis. The inflammatory factors released against the virus cause further tissue damage.[10] Endothelial damage causes hemostatic failure by activating the intrinsic coagulation cascade through platelet adhesion, aggregation, and degranulation. As a result, disseminated intravascular coagulation (DIC) and diffuse bleeding occur. DIC develops in CCHF as a result of excessive consumption of coagulation factors in plasma. As a consequence of hepatocyte damage, coagulation factors synthesized from the liver are also reduced.[11] DIC development resulted in 2 deaths in our study.

Petechiae and ecchymoses may be seen in CCHF patients. The most common sites of bleeding are the nose, gastrointestinal tract (melena, hematemesis, intraabdominal bleeding), gingiva, and the vaginal and subconjunctival areas. Some patients may have clouding of consciousness, such as confusion and agitation.[12] Similar symptoms were observed in our study.

As with other viral hemorrhagic fevers, thrombocytopenia may occur in CCHF. In particular, bicytopenia (leukopenia and thrombocytopenia) occurs frequently. Pancytopenia is less common. In the early stage, severe thrombocytopenia causes death.[13] Thrombocytopenia was also observed in all our patients and managed with medical interventions as appropriate.

Depending on the extent of liver damage, serum transaminases increase at varying degrees.[14] Hepatomegaly and splenomegaly findings were frequently observed in our patients. Therefore, we think that the elevated AST and ALT levels in fatal cases might have prognostic relevance. Although the viral load of the patients was not evaluated in our study, the relationship between viral load and prognosis was observed in previous studies. It might be suggested that high transaminase levels may develop as a result of increased viremia or a direct cytopathic effect. Recently, the use of ribavirin for the treatment of CCHF has become more common.[15]

Studies on rabbits have shown that TAFI inhibits fibrinolysis. TAFI may be the cause of atherothrombotic

disorders because of its effect on coagulation and the fibrinolytic system.[16] In a study by Eichinger et al.,[17] TAFI levels were measured in 600 patients. They observed that the risk of thromboembolism increased 2-fold with higher plasma TAFI levels. Sonmez et al.[6] suggested that low TAFI activity might disturb the regulation of fibrinolysis, and it might be used as a risk marker in CCHF. The aforementioned studies show that TAFI plays a central role in the balance between coagulation and fibrinolysis.

The endothelial cell receptor thrombomodulin increases the activation of TAFI by thrombin by approximately 1250-fold.[18] Our study showed that plasma TAFI activity was significantly lower in CCHF patients compared to controls. The decrease in TAFI activity may be explained by the disruption of the synthesis/clearance balance. Conditions such as DIC and sepsis may increase the consumption of TAFI by triggering excessive clotting activity and thrombin production.[19,20]

Despite its negative effects on the fibrinolytic system, TAFI has a regulatory effect on inflammation, blood pressure, and vascular tone. TAFI has drawn attention because of the effect of inflammation in cardiovascular diseases.[21] Park et al.[22] evaluated TAFI levels in 25 patients with sepsis (patients with fever, tachycardia, tachypnea, leukocytosis or leukopenia, and a positive culture) and argued that TAFI might be used as a healing criterion in patients diagnosed with sepsis, in post-treatment follow-up. Zeerleder et al.[20] investigated the TAFI antigen and the plasminogen activator inhibitor-1 (PAI-1) levels in 32 patients with severe sepsis and in 8 patients with septic shock. They found significantly lower TAFI levels in the patients with sepsis.

Hataji et al.[23] examined TAFI levels in patients with lung cancer and reported that the production and secretion of TAFI from the liver increased due to inflammatory cytokines secreted from cancer cells. Ozkan et al.[24] measured TAFI levels in 46 patients with active inflammatory bowel disease. They argued that thromboembolic events are multifactorial and TAFI cannot be used alone as an indicator of disease activity.

Donmez et al.[25] evaluated TAFI in patients with Behcet's disease. TAFI levels were higher in Behcet patients. Although CCHF is a vasculitis that can progress to sepsis, we found low plasma TAFI levels in our patients. This result is probably due to the fact that CCHF affects the liver more than Behçet's disease does.

Study limitations

First, the sample size was relatively small. Second, we could not evaluate the TAFI activity in our study. Third, we did not investigate the genetic polymorphisms of TAFI in CCHF patients.

Low TAFI activity may cause bleeding complications in CCHF patients by disrupting the fibrinolytic and coagulation cascades.

Ethics Committee Approval: The study complies with the Declaration of Helsinki and was approved by the Atatürk University Clinical Research Ethics Committee (2014/7-106).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

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