ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Epidemiological, Clinical and Laboratory Characteristics of Patients with Crimean-Congo Hemorrhagic Fever

Kırım Kongo Kanamalı Ateşli Hastaların Epidemiyolojik, Klinik ve Laboratuvar Özellikleri

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ABSTRACT Objective: Crimean-Congo hemorrhagic fever (CCHF) is the leading viral hemorrhagic fever, widely seen throughout the world. The aim of this study was to review CCHF patients followed up in Erzurum Oltu State Hospital. **Material and Methods:** A retrospective evaluation was made of the epidemiological characteristics and clinical findings of 57 patients who presented at our hospital between January 2011 and September 2012, and were diagnosed with CCHF, confirmed with reverse transcriptase polymerase chain reaction test. **Results:** The 57 patients comprised 33 (57.89%) males and 24 (42.11%) females with a mean age of 44.21±19.82 years (range, 5-77 years). The most CCHF cases were seen in May and June. A history of contact with animals was reported by 61.40% of the patients, a tick bite by 36.84% and one patient was infected from contact with the secretions of an infected patient. The complaints on presentation were mostly high fever, fatigue and headache. **Conclusion:** In a larger proportion of the patients, there is no history of a known tick bite. Therefore, in endemic regions, awareness should be raised through public education meetings giving information about people at particular risk, protection from the disease, symptoms, routes of infection, and means of protection.

Keywords: Epidemiology;
hemorrhagic fever virus, Crimean-Congo;
tick-borne diseases

ÖZET Amaç: Kırım-Kongo kanamalı ateşi (KKKA), dünyada yaygın olarak görülen viral kanamalı ateşlerin başında gelir. Bu çalışmada, Erzurum Oltu Devlet Hastanesi'nde izlenen KKKA olguları irdelenmiştir. **Gereç ve Yöntemler:** Nisan 2011 ve Eylül 2012 tarihleri arasında hastanemize başvuran ve ters transkriptaz polimeraz zincir reaksiyonu ile KKKA tanısı doğrulanan 57 hastanın epidemiyolojik özellikleri, klinik bulgularını retrospektif olarak değerlendirildi. **Bulgular:** Elli yedi olgunun 33'ü (%57,89) erkek, 24'ü (%42,11) kadındı. Yaş ortalaması 44,21±19,82 (minimum 5, maksimum 77) idi. KKKA vaka sayısı, en sık Mayıs ve Haziran ayında görüldü. Hastaların %61,40'ının hayvanlarla temas öyküsü varken, %36,84'ünde kene tutma öyküsü ve sadece 1 hastada, enfekte hastanın sekresyonu ile temas öyküsü mevcuttu. Hastaların başvuru şikâyetleri arasında en fazla yüksek ateş, hâlsizlik ve baş ağrısı saptandı. **Sonuç:** Hastalığın büyük bir kısmında, bilinen kene temas öyküsü bulunmamaktadır. Hastalığın endemik olarak görüldüğü bölgelerde, özellikle risk altındaki kişilere hastalıktan korunma, hastalığın semptomları, hastalığın bulaşma ve korunma yolları hakkında eğitim toplantıları düzenlenmeli ve farkındalık artırılmalıdır.

Anahtar Kelimeler: Epidemiyoloji;
hemorajik ateş virüsü, Kırım-Kongo;
kene kaynaklı hastalıklar

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal disease, characterised by fever and bleeding, which is caused by the CCHF virus, from the Nairovirus strain of the Bunyaviridae family.[1] The virus is carried by *Hyalomma marginatum* ticks. The virus is endemic in ticks in nature and circulates in the tick-vertebrate-tick cycle. Ticks function as both a reservoir and a vector for the virus.[2]

In endemic regions such as Turkey and Russia, the annual incidence is very high. The provinces in Turkey where the disease is seen most are Erzurum, Erzincan, Gümüşhane, Bayburt, Tokat, Yozgat, Sivas,

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Amasya, Çorum, Çankırı, Bolu, Kastamonu, Karabük, Giresun and Samsun.[3]

Just as infection may occur with a person being bitten by an infected tick, it can also occur through contact with a person in the acute phase or contact with the tissue or blood of an infected animal.[4]

The onset of CCHF is characterised by non-specific clinical symptoms of fatigue, widespread muscle and joint pain, headache, nausea, vomiting, diarrhea and fever.[5] In patients with a severe course, hepatosplenomegaly, vascular disorders and hemorrhage can develop. The laboratory test results initially show thrombocytopenia, leukopenia and high liver enzyme levels, and prolonged hemorrhagic markers. Mortality rates have been reported to vary between 4% and 20% depending on the geographic region and quality of the healthcare services available.[6]

The aim of this study was to retrospectively evaluate the clinical and epidemiological findings of patients with a confirmed diagnosis of CCHF at Erzurum Oltu State Hospital, northern Turkey.

MATERIAL AND METHODS

The study was carried out in accordance with the Helsinki Declaration principles. Approval for the study was granted by the Clinical Research Ethics Committee of Süleyman Demirel University Medical Faculty (decision no: 27.7.2016/137). Informed consent form was obtained from the patients. The study included 57 patients who presented at Erzurum Oltu State Hospital between April 2011 and September 2012 with findings consistent with CCHF (fatigue, bleeding, fever, leukopenia and thrombocytopenia). The diagnosis was confirmed with viral -RNA shown in a reverse transcriptase polymerase chain reaction test of a venous blood sample performed in Erzurum Hıfzıssıhha Laboratory. The patients with confirmed CCHF diagnosis were referred for treatment and follow up to the Erzurum CCHF reference hospital. Epidemiological characteristics and clinical findings were retrospectively evaluated.

STATISTICAL ANALYSIS

Data obtained in the study were analysed statistically using SPSS vn. 21.0 software. Missing value analysis was applied first and it was determined that there were no missing data from the data entered. In the descriptive analysis, frequency and percentages were calculated. Outliers for age variable was visually checked via boxplot. No significant outlier is determined. Additionally, the only continuous variable, which is age, is checked for normal distribution. Skewness and kurtosis values (-0.016 and -1.189 respectively) were both between the critic calues of -2 and +2 that suggest normal distribution.[7] On the contrary, data for age variable also tester violation of normal distribution, Shapiro-Wilk suggested that the data were not distributed normally ($p<0.05$). Since data is not normally distributed, the median and 25% and 75% percentage scores are calculated and reported as 25, 43, and 60 respectively. It must be noticed here that, this study does not use inferantial statistic of any kind such as regression, ANOVA, MANCOVA etc.; and normallity is not pre-requsite or assumption for conducting descriptive statistics, yet descriptive statistics might make more sense with the consideration of age distribution of the participants. Descriptive findings of the study are reported and discussed next.

RESULTS

The patients comprised 42.11% females and 57.89% males with a mean age of 44.21±19.82 years (range, 5-77 years). The distribution of the districts where the patients lived was 50.88% Oltu, 15.79% Olur, 31.58% Şenkaya, and 1.75% Yusufeli. The hospital departments where the patients first presented were the emergency department in 57.89% of cases, internal medicine polyclinic in 10.53%, infectious diseases polyclinic in 29.82%, and obstetrics and gynaecology in 1.75%.

The highest number of CCHF cases were seen in May and June. There was a history of contact with animals in 61.40% of the patients, 36.88% reported that they had been bitten by a tick and 1 patient had a history of contact with the secretions of an infected patient. Among these patients, there was no history of tick bite in 63.16%.

The most common complaints of the patients on presentation were high fever, fatigue and loss of appetite. The laboratory findings at the time of first

presentation were leukopenia in 92.98% of patients, thrombocytopenia in 96.49%, elevated aspartate aminotransferase (AST) in 71.93%, elevated alanine aminotransferase (ALT) in 43.86%, elevated creatine kinase (CK) in 63.16% and elevated lactate dehydrogenase (LDH) in 78.95%. Various clinical symptoms, demographic characteristics and the laboratory test results at the time of presentation are shown in Table 1.

Two patients were deceased one of which was the patient with a history of contact with the secretions of an infected patient. A total of 55 patients were discharged from hospital with medication.

DISCUSSION

CCHF, which originates from ticks, is one of the most commonly seen viral infections in the world. It is a potentially fatal disease widely seen in Asia, Africa and Europe.[4] Animals play a critical role in the life-cycle of CCHF with proliferation of the virus before it is spread to humans from ticks.[8]

The first reported case in Turkey was in 2002, in the Kelkit valley in the province of Tokat, northern Turkey.[9] The Ministry of Health in Turkey treats CCHF as an important public health problem, especially in the north-east Anatolia region, where it is endemic.

In recent years, sporadic cases have been reported in almost all regions of Turkey. It can be seen that the majority of the reported CCHF cases were more exposed to the tick population as they were involved in agriculture and animal husbandry. Changes in climate conditions are one of the factors facilitating proliferation of the tick population and are thought to have increased the frequency of tick-borne infectious diseases.[10] In Turkey the disease is seen between may and September, reaching a peak in July.[11] In the current study, the highest number of cases were seen in the months of May (26.32%) and June (29.82%).

Although there has been no evidence of any disease caused by the virus in animals, many patients diagnosed with CCHF have a history of working with or contact with animals and approximately 60% have a history of tick bite.[10] In a study by Yilmaz et al.,

TABLE 1: Demographic, clinical and laboratory features of patients followed with Crimean-Congo hemorrhagic fever diagnosis.

Characteristic	n (%)
Sex	
Male/Female	33 (57.90)/24 (42.20)
Mean age	44.21±19.82 (minimum 5, maximum 77)
Application months	
April	6 (10.53)
May	15 (26.32)
June	17 (29.82)
July	10 (17.54)
August	8 (14.04)
September	1 (1.75)
Living environment	
Oltu	29 (50.88)
Olur	9 (15.79)
Senkaya	18 (31.58)
Yusufeli	1(1.75)
Departments they apply in the hospital	
Emergency	33 (57.89)
Internal medicine	6 (10.53)
Infectious diseases	17 (29.82)
Gynecology and obstetrics	1(1.75)
Contact history	
Tick bite	21 (36.84)
Contact with blood/body fluids of infected people	1 (1.75)
Contact with animal blood/tissue and other body fluid	35 (61.40)
Clinical findings	
Weakness	25 (43.86)
Nausea/vomiting	13 (22.81)
Headache	18 (31.58)
Fever	55 (96.49)
Diarrhoea	8 (14.04)
Widespread body pain	14 (24.56)
Abdominal pain	18 (31.58)
Hemorrhagic manifestations	4 (7.02)
Result	
Healing	55 (96.49)
Exitus	2 (3.51)
Laboratory findings	
Leukopenia	53 (92.98)
Thrombocytopenia	55 (96.49)
AST elevation	41 (71.93)
ALT elevation	25 (43.86)
CK elevation	36 (63.16)
LDH elevation	45 (78.95)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK: Creatinine phosphokinase; LDH: Lactate dehydrogenase.

68.90% of CCHF cases had a history of tick bite or contact with ticks and 61.70% had been in close contact with animals. One case was an infant who had become infected while breastfeeding.[12] Sağmak Tartar et al. reported that 72.10% of a series of 61 patients had a history of tick bite.[13]

In the current series, 36.84% had no history of tick bite, and 61.44% reported contact with animals. Only one case had a history of infection from patient secretions. As a significant proportion of the current cases had no history of known tick bite, educational meetings should be organised in endemic regions for the public and all healthcare workers in respect of the symptoms and findings of the disease and awareness should be increased.

According to Ministry of Health data, of the 1,820 cases determined with CCHF between 2002 and 2007 in Turkey, 53% were male and 62% had a history of contact with animals. The mean age of patients was 44 years (range, 1-92 years), 34% of the patients were farmers and 36.40% were housewives.[12] CCHF is seen in the actively working age group and those with the possibility of exposure to ticks. Mourya et al. defined male gender, and close contact with a CCHF case as high risk factors for CCHF infection.[14] Of the 57 cases diagnosed with CCHF in the current study, 57.89% were male and 42.11% were female, all housewives. The mean age of the cases was 44.20 years (range, 5-77 years). The reason for the high rate of CCHF in housewives in this study can be attributed to the fact that women living in rural locations contibute to agriculture and livestock care and are therefore exposed to ticks.

Patients with CCHF may present with tables varying symptoms from mild to severe. Generally the clinical symptoms and findings on presentation are non-specific. These symptoms include fatigue (92.30%), sudden onset of fever (89.40%), widespread muscle pain (69.70%), severe headache (68.10%), nausea-vomiting (64.70%) and hemorrhagic symptoms such as maculopapular rash, petechiae, purpura, ecchymosis and epistaxis (23%).[12]

Headache is a frequently seen symptom on presentation. In a study by Krasniqi et al., headache was reported on presentation in 25 (93%) of 27 patients diagnosed with CCHF, and in another study by Çevik et al., the symptom of headache was reported in 39 of 58 cases with a fatal course and in 6 of 11 cases with a non-fatal course.[15,16] In the current study, 18 (31.58%) patients had headache at the time of presentation, 25 (43.86%) had symptoms of fatigue, and 14 (24.56%) had widespread body pain.

Another finding of CCHF is organomegaly. Duru and Fışgın reported hepatomegaly and splenomegaly in approximately 30% of CCHF patients.[17] Hepatomegaly and splenomegaly were not determined in any case of the current study.

Of the laboratory tests performed on presentation, thrombocytopenia, leukopenia, and elevated AST, ALT, LDH and CK levels are common.[18] Increased myeloperoxidase expression in leukocytes leads to increased leukocyte lysis. Therefore, leukopenia in CCHF patients may be attributable to lysis.[19] In an epidemiological study by Yilmaz et al., leukopenia was determined in 88.90% of patients on presentation. In the current study, leukopenia was present in 93% of cases.[12]

Thrombocytopenia, hypofibrinogenemia, and increased activated partial thromboplastin time (aPTT) and prothrombin time (PT) are observed in almost all cases. These abnormalities are highest during a hemorrhage.[10] At the same time, leukopenia and hepatocellular cytolysis are often seen. Several studies have shown that as the degree of thrombocytopenia increases, there is a decrease in PT and a worse prognosis for prolonged aPTT.[20] Sahak et al. reported thrombocytopenia or thrombocyte count <50,000 in 55% of CCHF cases.[21] In another study, thrombocytopenia was reported at the rate of 78%.[22] In the current study, thrombocytopenia was determined in 96.49% of the cases.

In the study of Ertugrul et al., thrombocytopenia and leukopenia were reported to be seen in 65% of cases, elevated ALT and AST in 77%, elevated LDH in 69%, and elevated CK in 42%.[23] In a study by Ozkurt et al. of 60 CCHF patients between 2002 and 2004, it was reported that ALT and AST were elevated in all the patients and the AST values were higher than the ALT values. In the patients with mortality in the same study, the mean ALT, AST, LDH,

CK, PTT, INR and urea values were higher and the thrombocyte count was lower.[11]

In the current study, elevated AST was determined in 71.93% of cases, elevated ALT in 43.86%, elevated CK in 63.16% and elevated LDH in 78.95%. From these data, it might be considered that as the findings of CCHF are non-specific, leukopenia and thrombocytopenia are more meaningful than ALT and AST values in the diagnosis of the disease in endemic regions.

In a study in South Africa, leukocyte count $<10x10^9$ /L, thrombocyte count $<20x10^9$/L, AST >200 U/L, ALT >150 U/L, aPTT >60 s, and fibrinogen values <110 mg/dL in the first 5 days of the disease were reported to be a marker of mortality in CCHF cases.[24] Ergonul et al. stated that ALT and AST values did not conform with severe CCHF criteria and there should be correction to AST >700 IU/L and ALT >900 IU/L.[25]

In a study of 32 CCHF cases between 2013 and 2016, Ahmeti et al. reported that 11 cases died, and of the laboratory parameters, viral load >1×108.5 copy/mL, LDH >2,200 U/mL and leukocyte count >7,700 cells/μL were associated with mortality. In the same study, there was seen to be a non-significant trend to corresponding dependence between mortality and thrombocyte count <50,000/μL (p=0.057), and no relationship was reported to have been found between mortality and ALT, AST, and other laboratory parameters.[26]

Bakir et al. reported that in patients who developed mortality, the laboratory values of INR, AST, LDH and CK were higher, splenomegaly and impaired consciousness were seen as examination findings and these were predictive factors as a marker of mortality.[27] In the 2 cases of the current study who developed mortality, the values were determined as AST >500 IU/L, ALT >700 IU/L and thrombocyte count <30,000/μL.

According to Ministry of Health data, a total of 9,069 CCHF cases were reported in Turkey in the period 2002-2014, and of these, 440 developed mortality.[28] Thus, the mortality rate for CCHF cases in Turkey between 2002 and 2014 was approximately 5%.[29] The Ministry of Health reported that in 2017, 16 of 343 cases were lost.[28]

In previous studies, various mortality rates have been reported; 15% in a 10-year study by Durrani et al. 20% by Khurshid et al. 2% by Chinikar et al. and 5% by Bodur et al.[22,30-32] In a study which examined the clinical and epidemiological characteristics of CCHF occurring in Herat state in Afghanistan, the mortality rate was reported to be 22% in 63 CCHF cases hospitalised in 2017.[33]

The difference in mortality rates is thought to be associated with phylogenetic variations and the route of infection and the level of knowledge of the community about CCHF.[34] The mortality rate in Turkey is relatively lower than that of other countries.[29] The mortality rate of 3.51% in the current study was lower than rates reported in literature. One of the cases that died was a nososocomial infection from an infected person. The mortality rates of nosocomial CCHF cases that develop following contact with infected patients have been reported to be higher than those of CCHF cases which have developed following a tick bite.[35]

CONCLUSION

CCHF has been reported from almost every region of Turkey. As seen in the current study, in a larger proportion of patients, there has been no known contact with ticks. In patients presenting in endemic regions with sudden onset of fever, fatigue, leukopenia and thrombocytopenia in laboratory findings, impairment in coagulation tests and elevated liver enzymes and CK levels, CCHF should come to mind. In regions where the disease is endemic, awareness should be raised through public education meetings giving information about protection from the disease for people at particular risk, symptoms, routes of infection, and means of protection.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise,

working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Semiha Orhan;* ***Design:*** *Semiha Orhan;* ***Control/Supervision:*** *Semiha Orhan;* ***Data Collection and/or Processing:*** *Semiha Orhan;* ***Analysis and/or Interpretation:*** *Semiha Orhan, Kemal Yetiş Gülsoy;* ***Literature Review:*** *Semiha Orhan, Kemal Yetiş Gülsoy;* ***Writing the Article:*** *Semiha Orhan, Kemal Yetiş Gülsoy;* ***Critical Review:*** *Semiha Orhan, Kemal Yetiş Gülsoy;* ***References and Fundings:*** *Semiha Orhan;* ***Materials:*** *Semiha Orhan.*

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