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Clinical and laboratory features of Crimean-Congo hemorrhagic fever: predictors of fatality

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Summary
Objective: To determine the predictors of fatality among patients with Crimean-Congo hemorrhagic fever (CCHF) based on epidemiological, clinical, and laboratory findings.
Methods: Among the patients with possible CCHF who were referred to Ankara Numune Education and Research Hospital (ANERH) from the surrounding hospitals between 2003 and 2006, those with IgM antibodies and/or reverse transcriptase-polymerase chain reaction (RT-PCR) results positive for CCHF virus in their blood, and who had received only supportive treatment, were included in the study.
Results: Sixty-nine patients with CCHF were admitted to ANERH from various cities of the northeastern part of the central region and southern parts of the Black Sea region of Turkey. Eleven (15.9%) patients died. Age, gender, days from the appearance of symptoms to admission, and initial complaints except bleeding were similar between fatal and non-fatal cases ($p > 0.05$). Among the clinical findings, ecchymosis ($p = 0.007$), hematemesis ($p = 0.030$), melena ($p < 0.001$), somnolence ($p < 0.001$), and gingival bleeding ($p = 0.044$) were more common among fatal cases. The mean platelet count was 47.569×10^9/l in non-fatal cases and 12.636×10^9/l in fatal cases ($p = 0.003$). Among the fatal cases, the mean prothrombin time (PT; 18.4 s vs. 13.4 s; $p < 0.001$) and the mean activated partial thromboplastin time (aPTT; 69.4 s vs. 42.7 s; $p = 0.001$) were longer, and the mean alanine aminotransferase (ALT; 1688 vs. 293; $p < 0.001$), mean aspartate aminotransferase (AST; 3028 vs. 634; $p < 0.001$), mean lactate dehydrogenase (LDH; 4245 vs. 1141; $p < 0.001$), mean creatine phosphokinase (CPK; 3016 vs. 851; $p = 0.004$) levels and the mean international normalized ratio (INR; 1.38 vs. 1.1; $p < 0.001$) were higher. In a Cox proportional hazards model, thrombocytopenia of $\leq 20 \times 10^9$/l (hazard rate (HR) 9.67; 95% confidence interval (CI) 1.16—80.68; $p = 0.036$), a prolonged aPTT $\geq$60 s (HR 11.62; 95% CI 2.40—56.27; $p = 0.002$), existence of melena (HR 6.39; 95% CI 1.64—24.93; $p = 0.008$), and somnolence (HR 6.30; 95% CI 1.80—22.09; $p = 0.004$) were independently associated with mortality.

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Conclusions: Thrombocytopenia of $\leq 20 \times 10^9$/l, a prolonged aPTT $\geq$60 s, the existence of melena, and somnolence were independent predictors of fatality.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is caused by a Nairovirus belonging to the genus Bunyavirus of the family Bunyaviridae, and transmitted to humans by Hyalomma ticks or by direct contact with the blood of infected humans or domestic animals.[1,2] The most common clinical signs of CCHF are fever, nausea, headache, diarrhea, myalgia, petechial rash, and bleeding.[3]

At present, CCHF is a public health problem in many regions of the world including Asia, Eastern Europe, Africa, and Russia.[4] CCHF is a severe disease in humans with a fatality rate of up to 80%, most deaths occurring 5 to 14 days after the onset of illness.[3–5] Since 2002, a rapid emergence of CCHF has occurred in the central, northern, and eastern regions of Turkey.[6–8] By the end of 2006, there had been 1103 confirmed CCHF cases and 59 (5.4%) deaths in Turkey.[9]

This study was undertaken to determine the predictors of fatality among patients with CCHF based on epidemiological, clinical, and laboratory findings.

Methods

This prospective study was carried out at Ankara Numune Education and Research Hospital (ANERH), a referral and tertiary-care hospital in Turkey. Several patients with possible CCHF were referred to ANERH from the surrounding hospitals during the spring and summer seasons of the years 2003 to 2006. Only patients with a definitive diagnosis of CCHF by means of clinical presentation plus the presence of specific IgM antibody and/or detection of viral RNA by reverse transcriptase-polymerase chain reaction (RT-PCR), and patients who had received only supportive treatment, were included in the study. Biochemical and hematological laboratory parameters were measured on a daily basis after admission to the hospital. Data were recorded prospectively on individual forms.

Patients were given preparations of erythrocytes, platelets, and fresh frozen plasma depending on their homeostatic state. Patients who received antiviral therapy were excluded from the study as antiviral therapy might have changed the course of the disease.

Statistical analysis

The Student's *t*-test was used for independent and paired continuous variables, and proportion comparisons for categorical variables were done using Chi-square tests, although Fisher's exact test was used when data were sparse. A *p*-value of <0.05 was considered statistically significant. Survival curves with a 95% confidence interval were computed using the Kaplan–Meier method. Cox regression was used to model outcomes. The time start-point was the onset of complaints and the time end-point was either death or discharge from the hospital. For multivariate analysis, only variables with a *p* value <0.05 were entered into a Cox proportional hazards model and selected using a stepwise selection procedure. Hazard ratios (HR) and 95% confidence intervals (95% CI) were computed from estimated parameters of the final regression model. Software package Stata 9.0 (College station, Texas, USA) was used for the analysis.

Results

Sixty-nine patients were enrolled in the study. These patients were from various cities of the northeastern part of the central region and southern parts of the Black Sea region of Turkey. Their mean age was 50 years, and 45 patients (65.2%) were male. Fifty-four (78.3%) patients were involved in farming/handling livestock. A history of tick bite was present for 37 (53.6%) patients.

The patients showed hemorrhagic signs including epistaxis (26.1%), petechiae (20.3%), ecchymosis (17.4%), melena (17.4%), gingival bleeding (15.9%), hematemesis (13.0%), hematuria (5.8%), and hematoma (2.9%). Other prominent clinical signs were fever, anorexia, myalgia, and headache. Almost all of the patients had leukopenia, thrombocytopenia, and elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) levels at the time of admission.

Forty patients were IgM positive and 50 patients were RT-PCR positive. Seven (63.6%) out of the 11 fatal cases were only RT-PCR positive.

The case–fatality rate was 15.9%. Fatal cases were hospitalized for a mean of 3.8 days (range 1–9) before death. The duration of hospitalization was approximately 8 days (range 2–19) in non-fatal cases. The disease started a mean of 6.3 days (range 2–10) before hospitalization in fatal cases and 5.8 days (range 1–15) in non-fatal cases.

Age, gender, number of days from the appearance of symptoms to admission, and initial complaints except bleeding were similar between fatal and non-fatal cases ($p > 0.05$). Among the clinical findings, ecchymosis ($p = 0.007$), hematemesis ($p = 0.030$), melena ($p < 0.001$), somnolence ($p < 0.001$), and gingival bleeding ($p = 0.044$) were more common among fatal cases (Table 1).

In fatal cases, the mean heart rate was 89 bpm (range 80–112) and in non-fatal cases 86 bpm (range 62–120) ($p = 0.483$). Blood pressure was normal in all patients at the time of admission.

The mean platelet count was 47.569×10^9/l in non-fatal cases and 12.636×10^9/l in fatal cases ($p = 0.003$). Among the fatal cases the mean prothrombin time (PT; 18.4 s vs. 13.4 s; $p < 0.001$) and mean activated partial thromboplastin time (aPTT; 69.4 s vs. 42.7 s; $p = 0.001$) were longer, and the mean ALT (1688 vs. 293; $p < 0.001$), mean AST (3028 vs. 634; $p < 0.001$), mean LDH (4245 vs. 1141; $p < 0.001$), mean CPK