Evaluation of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever and comparison of characteristics in patients admitted to a secondary care hospital in Kastamonu, Turkey.

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Abstract:

Background: Crimean-Congo hemorrhagic fever (CCHF) is an endemic disease in Turkey. The clinical presentation and laboratory findings are not specific especially in cases without hemorrhagic findings.

Objective: We aimed to evaluate CCHF cases and compare them with non-CCHF cases in terms of their characteristics during admission.

Methods: Cases with a preliminary diagnosis of CCHF at a secondary care hospital in Kastamonu in 2013 were evaluated, retrospectively. Cases testing RNA/IgM positive were considered as CCHF. Cases testing both RNA and IgM negative were considered as non-CCHF. The two groups were then compared in terms of their clinical, laboratory and epidemiological characteristics during admission.

Results: A total of 41 cases were tested and CCHF was found in 46.3% of cases. Fatality was 5.3% in CCHF cases. The frequency of tick bites and CK elevation in CCHF cases was significantly higher than non-CCHF cases (p<0.05). There were no significant differences between the two groups regarding other characteristics (p>0.05).

Conclusions: In cases with a preliminary diagnosis of CCHF, especially in cases without a history of tick bite and with normal CK levels during admission, performing tests for the differential diagnosis may be advisable without waiting for the results of tests for CCHF.

Keywords: Crimean-congo hemorrhagic fever, Kastamonu, Turkey

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Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral zoonotic infection acquired by a tick bite, transmitted from body fluids or blood of domestic animals and cases with CCHF virus (CCHFV); this virus belongs to the genus Nairovirus in the family Bunyaviridae. The clinical spectrum of the disease varies from a subclinical infection to severe disease and death, with a reported fatality rate of 15–30% in human cases. It was reported in the Crimean Peninsula in 1944 for the first time. Since then, CCHF has been reported from different parts of Africa, Eastern Europe, the Balkans, the Middle East, Central and Southern Asia. The first case of CCHF infection in Turkey was reported in the Kelkit Valley region in 2002.

Turkey has become the country with the highest number of CCHF cases among the countries that report CCHF cases annually. This infection is an endemic zoonosis appearing every year during spring and summer in Turkey with approximately 1000 cases reported annually. Majority of cases in Turkey were from 15 cities in Kelkit Valley and its environs including Kastamonu Province. CCHF cases from countries that border Turkey including Bulgaria, Greece, Iran and Iraq have also been reported. According to various studies, the fatality rate of CCHF ranged from 15-30%. However, the crude fatality rate was 5% in 2002-2007 according to the reports of the Turkish Ministry of Health surveillance.

There are a few studies evaluating cases with a preliminary diagnosis of CCHF and reporting the rate of confirmed CCHF cases among suspected CCHF cases. This rate ranges between 21% and 57%. In this study, cases of CCHF admitted to a secondary care hospital in Kastamonu in 2013 were evaluated in terms of their clinical, laboratory and epidemiological characteristics. Cases with CCHF were also compared in terms of these characteristics with non-CCHF cases whose reverse transcriptase-polymerase chain
reaction (RT-PCR) and ELISA IgM tests were negative for CCHFV.

**Methods**

In 2013, cases admitted with a preliminary diagnosis of CCHF to the Dr Münif Islamoğlu Hospital (Kastamonu Province, Turkey) were included in this study. A preliminary diagnosis of CCHF was made if cases presented with at least two of: (a) sudden onset of high-grade fever; (b) headache; (c) weakness; (d) nausea and vomiting; (e) diarrhea; and one of: (a) thrombocytopenia (platelet count of <150 x 10^9/L); and/or (b) leucopenia (white blood cell count of <4 x 10^9/L); and also one of: (a) history of tick bite; (b) close contact with animals; (c) living in rural areas or travelling to rural areas; (d) being a laboratory worker; or (e) contact with people with similar symptoms in the past 15 days.

Serum samples of all cases were collected within 24 hours of admission and were sent to the Public Health Institution of Turkey, National Virology Reference Laboratory to determine CCHF IgM antibodies by ELISA and CCHFV RNA by RT-PCR. ELISA was not performed on serum samples already detected by RT-PCR as positive for viral RNA. Cases with viral RNA or IgM antibody positivity were considered as CCHF cases. Cases with both viral RNA and IgM antibody negative were considered as non-CCHF cases.

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Serum samples of cases with a preliminary diagnosis of CCHF were followed up at our hospital. Three had a positive IgM by ELISA and 16 cases had a positive RT-PCR for CCHFV RNA. A total of 19 cases (46.3%) were diagnosed with definite CCHF. The remaining 22 cases (53.7%) were found negative by both tests and were considered as non-CCHF cases. 52.6% (10) of the CCHF cases were female, while 47.4% (9) were male. Besides, 54.5% (12) and 45.5% (10) of the non-CCHF cases were female and male, respectively. The median age of CCHF cases and non-CCHF cases was 54.0 (16-83) and 51.5 (20-78), respectively. There were no statistically significant differences between the two groups regarding gender and age (p> 0.05). Six cases from the CCHF group were transferred to a tertiary care hospital. One of the transferred CCHF cases died while the other 18 cases were cured. Case who died was a 42 years old female patient with no comorbid diseases and the cause of her death was multi organ failure. She did not receive ribavirin therapy. Thus, fatality rate was 5.3% (1/19) in the CCHF group. Moreover, there were no pediatric cases with a definite diagnosis of CCHF in our hospital in 2013. CCHF cases were evaluated retrospectively in terms of their clinical and laboratory features during admission to the hospital and epidemiological features within 15 days, and these characteristics of CCHF cases were compared with non-CCHF cases.

Statistical analysis was performed using SPSS version 15—0 (SPSS Inc., USA). Descriptive statistics (median, minimum and maximum value, mean and standard deviation, count and percentage) were used to summarize the results. Nominal variables were compared using χ2 test with Yates’ correction and Fisher’s exact test. Continuous variables were compared using Mann Whitney U test. When a p-value was found less than 0.05, the result was considered as statistically significant and the null hypothesis was rejected.

**Results**

In 2013, a total of 41 cases with a preliminary diagnosis of CCHF were followed up at our hospital. Three had a positive IgM by ELISA and 16 cases had a positive RT-PCR for CCHFV RNA. A total of 19 cases (46.3%) were diagnosed with definite CCHF. The remaining 22 cases (53.7%) were found negative by both tests and were considered as non-CCHF cases. 52.6% (10) of the CCHF cases were female, while 47.4% (9) were male. Besides, 54.5% (12) and 45.5% (10) of the non-CCHF cases were female and male, respectively. The median age of CCHF cases and non-CCHF cases was 54.0 (16-83) and 51.5 (20-78), respectively. There were no statistically significant differences between the two groups regarding gender and age (p> 0.05). Six cases from the CCHF group were transferred to a tertiary care hospital. One of the transferred CCHF cases died while the other 18 cases were cured. Case who died was a 42 years old female patient with no comorbid diseases and the cause of her death was multi organ failure. She did not receive ribavirin therapy. Thus, fatality rate was 5.3% (1/19) in the CCHF group. Three of the transferred cases in the CCHF group and none of non-CCHF cases received oral ribavirin.

When looking at the monthly distribution of the CCHF cases, it was shown that the first case was detected in April and the highest number of cases was admitted in May (Figure 1).

Five cases were from Daday and four cases were from Devrekani and Taskopru which are districts of Kastamonu. The distribution of cases with a preliminary diagnosis of CCHF by districts is shown in Figure 2.

![Figure 1: Monthly distribution of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever.](image1.png)

![Figure 2: The distribution of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever by districts.](image2.png)
In both groups, the most common clinical symptoms during admission were weakness, widespread muscle pain, fever, headache, nausea and vomiting, respectively. The frequency of abdominal pain, diarrhea and maculopapular rash was higher in CCHF cases. Bleeding was observed in four (18.2%) cases in the non-CCHF group during admission. There was no bleeding during admission in the CCHF group. There were no statistically significant differences between the two groups in terms of clinical symptoms during admission (p>0.05) (Table 1).

Table 1: Clinical symptoms of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever during admission.

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>CCHF cases (19)</th>
<th>Non-CCHF cases (22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>100 (19)</td>
<td>95.5 (21)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Widespread muscle pain</td>
<td>94.7 (18)</td>
<td>86.4 (19)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Fever</td>
<td>84.2 (16)</td>
<td>72.7 (16)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Headache</td>
<td>42.16 (16)</td>
<td>68.2 (15)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>36.8 (7)</td>
<td>31.8 (7)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>36.8 (7)</td>
<td>18.2 (4)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36.8 (7)</td>
<td>18.2 (4)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>26.3 (5)</td>
<td>26.3 (4)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Altered level of consciousness</td>
<td>10.5 (2)</td>
<td>4.5 (1)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.0 (0)</td>
<td>18.2 (4)</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

* Includes hematoma, hemoptysis, hematuria and nose, gingival, vaginal, gastrointestinal, intra-abdominal and intracranial bleeding.

The most common physical finding during admission was fever, which was present in 68.4% (13) of CCHF and 50% (11) of non-CCHF cases. In the CCHF group, five (26.3%) cases had maculopapular rash, two (10.5%) had altered level of consciousness and hypotension, and one (5.3%) had ecchymosis, petechiae and tachycardia during admission. In the non-CCHF group, four (18.2%) cases had hemorrhagic findings, three (13.6%) had tachycardia, two (9.1%) had ecchymosis and hypotension, and one (4.5%) had maculopapular rash and altered level of consciousness. There was no statistically significant difference between the two groups in terms of physical findings during admission (p>0.05). The most common laboratory findings in the cases with a preliminary diagnosis of CCHF were thrombocytopenia, leukopenia, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation, respectively. 94.7% (18) of CCHF group and 95.5% (21) of non-CCHF group had thrombocytopenia. The proportion of cases with platelet counts between 150-101 x 10^9/L, 100-51 x 10^9/L and <51 x 10^9/L was 26.3% (5), 52.6% (10) and 15.8% (3) in the CCHF group and 54.5% (12), 27.3% (6) and 13.6% (3) in the non-CCHF group, respectively.

While elevated creatine phosphokinase (CK) and lactate dehydrogenase (LDH) levels were detected more frequently in the CCHF group, anemia was detected more frequently in the non-CCHF group. Thrombocytopenia was more frequently in the CCHF group, anemia was detected more frequently in the non-CCHF group. The frequency of CK elevation in CCHF cases (57.9%) during admission was significantly higher than non-CCHF cases (22.7%) (p<0.05). Other laboratory findings were similar between the two groups (p>0.05) (Table 2).

Table 2: The distribution of the laboratory findings of cases with a preliminary diagnosis of Crimean-Congo hemorrhagic fever during admission.

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>CCHF cases (19)</th>
<th>Non-CCHF cases (22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>94.7 (18)</td>
<td>95.5 (21)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Platelet count ranges:</td>
<td></td>
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</tr>
<tr>
<td>150-101 x 10^9/L</td>
<td>26.3 (5)</td>
<td>54.5 (12)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>100-51 x 10^9/L</td>
<td>52.6 (10)</td>
<td>27.3 (6)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>50,000-0 x 10^9/L</td>
<td>15.8 (3)</td>
<td>13.6 (3)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>89.5 (17)</td>
<td>63.6 (14)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>AST-ALT elevation</td>
<td>84.2 (16)</td>
<td>59.1 (13)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>LDH elevation</td>
<td>68.4 (13)</td>
<td>59.1 (13)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>CK elevation</td>
<td>57.9 (11)</td>
<td>22.7 (5)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Anemia</td>
<td>47.4 (9)</td>
<td>63.6 (14)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>INR elevation</td>
<td>38.8 (7)</td>
<td>22.7 (5)</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

When the cases were evaluated according to their occupations, majority were farming-animal husbandry with 68.2% (15) and 73.7% (14) in the CCHF and the non-CCHF groups, respectively. The remaining cases had no occupational risk. Among CCHF cases, 94.7% (18) were living in rural areas, 89.5% (17) had contact with animals and 84.2% (16) had a history of tick bite within 15 days before the onset of symptoms. In non-CCHF cases, these proportions were 86.4% (19), 77.3% (17) and 27.3% (6), respectively. In CCHF cases, a history of tick bite in the last 15 days was significantly higher than non-CCHF cases (p<0.05). Statistically significant differences were not found between the two groups in terms of other epidemiological characteristics (p>0.05) (Table 3).
The mean incubation period of cases with tick exposure was 3.8 ± 3.3 days in the CCHF group. The median day of illness on which patients were admitted was 0.6 to 1.5 days after the onset of symptoms. Seroprevalence was 10% in individuals with a history of farming, animal husbandry, and contact with animals and 36.4% in those with a history of tick bite.

In the CCHF group, the elapsed time was significantly higher than that in the non-CCHF group (p < 0.05). The fatality rate of CCHF was approximately 15–30% in 2005–2009. In our hospital, CCHF cases were diagnosed in 2005–2010 and the fatality rate of CCHF was approximately 5%.

In some studies, thrombocytopenia, leukopenia, increased AST-ALT, CK and LDH levels are the most common laboratory findings in CCHF cases. In our study, thrombocytopenia, increased AST-ALT and LDH levels were reported more commonly among cases with CCHF than non-CCHF cases, but, a history of tick bite was similar between the two groups in Bolu, Turkey. We found that the frequency of tick bites was significantly higher in CCHF cases than non-CCHF cases (p < 0.05).

The efficacy of ribavirin in antiviral treatment remains controversial. Although most reports claimed a therapeutic benefit, the quality of the evidence was low. In general, treatment of CCHF is mainly supportive therapy. In our study, the case who died did not receive ribavirin therapy and three of CCHF cases received oral ribavirin.

This study has several limitations. First, the study reports a retrospective, one-year, single center data and includes only participants who were admitted to our hospital. Second limitation is small sample size and low study power. Significant differences between the two groups may have not been detected. Third, the study evaluates characteristics of cases during admission, the patients were not evaluated during the course of the disease. Despite these limitations, all patients admitted to our hospital were included in the study. There are a few studies evaluating cases with a preliminary diagnosis of CCHF, but, a history of tick bite was similar between the two groups in Bolu, Turkey. We found that the frequency of tick bites was significantly higher in CCHF cases than non-CCHF cases (p < 0.05).

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The disease still remains important in endemic regions of Turkey, although the fatality rate is low (5%) in Turkey compared to other endemic countries. In areas without hemorrhagic findings, the clinical presentation is not diagnostic and physical examination and laboratory findings are not specific especially in cases without hemorrhagic findings. In areas endemic for CCHF, clinicians should be aware of the possibility of other diseases in cases with a preliminary diagnosis of CCHF and should determine and consider clinical, laboratory and epidemiological characteristics during admission of such cases.

**Conclusion**

In cases with a preliminary diagnosis of CCHF without a history of tick bite and with normal CK levels during admission, performing tests for the differential diagnosis may be advisable without waiting for the results of RT-PCR and ELISA tests for CCHF. This may help reduce the number of cases misdiagnosed as CCHF and increase the overall probability of detecting CCHF cases.

**References**