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Crimean-Congo hemorrhagic fever in children

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ABSTRACT

Background: Crimean-Congo hemorrhagic fever (CCHF) virus causes a severe disease in humans with a mortality up to 30%. In Turkey there has been an increase in the number of cases during years since 2002. Humans of all ages living in endemic areas, especially those who are working as shepherds and toddlers, have high risk of acquiring CCHF.

Objectives: The epidemiological, clinical, and laboratory characteristics of the children, who were diagnosed as Crimean-Congo hemorrhagic fever (CCHF) were described.

Study design: The children infected with CCHF virus between April 2008 and October 2009, and hospitalised in Ankara Dışkapı Children's and Research Hospital were included.

Results: Laboratory diagnosis was set by detection of CCHF IgM antibodies and/or genetic detection of CCHF virus. Thirtyone cases included to the study, and all were from the northeastern Anatolia and the southern parts of Black sea region. The mean age was 9.45 ± 4.9 years, the proportion of females was 38.7%. The majority (87%) of the cases had the history of tick bite. There was no fatal case. All the patients had the history of fever. Malaise, tonsillopharyngitis, nausea-vomiting, headache, diarrhea, myalgia and rash were the most common symptoms. The mean AST and ALT levels on the admission were 116 (range 25–389) and 61 (range 8–180) U/L respectively. The mean platelet count on admission was $125,000/\text{mm}^3$, and the lowest was $23,000/\text{mm}^3$. The mean of the lowest white blood cell count was $2353/\text{mm}^3$ and the mean of the highest lactate dehydrogenase was 861 IU/L.

Conclusions: The clinical course of CCHF among children seems to be milder than in adults. Tonsillopharyngitis is a common symptom among children with CCHF.

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1. Background

Crimean-Congo hemorrhagic fever (CCHF) is an often-fatal viral infection described in about 30 countries over the world, and it has the most extensive geographic distribution among the medically significant tickborne viruses.¹ Geographic distribution of CCHF closely approximates the known world distribution of *Hyalomma* spp. ticks. Humans of all ages living in endemic areas, especially those who are working as shepherds and toddlers, have high risk of acquiring CCHF.^{2,3} The virus belongs to the genus Nairovirus in the Bunyaviridae family and causes severe diseases in humans, with the reported mortality rate of 5–30%.^{4,5} In Turkey, the first cases of CCHF were diagnosed in 2002,^{6,7} and by the year 2008 about 3000 patients with the 5% case fatality rate (CFR) had been reported by the Ministry of Health of Turkey.

The CFR differs in different countries and different hospital settings. The host factors could be one of the factors for different CFR. Different age groups as one of the parameter of host factors are not detailed yet.^{8,9} Here, we present characteristics of children, who had been infected with CCHF. Knowledge of the differences in clinical and laboratory findings between adult and children cases might be useful in investigation.

2. Objective

The aim of this study is to evaluate the epidemiological, clinical, and laboratory characteristics of the children, who were diagnosed as CCHF.

3. Study design

3.1. Patient population

The patients with acute febrile syndrome characterized by fever, malaise, bleeding, leukopenia, and thrombocytopenia in spring and summer months of 2008 and 2009 were included. The patients,

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Table 1
Demographic and clinical characteristics of the children with CCHF.

	n (%)
Male/females ratio	1.6:1
Mean age, years (range)	9.4 ± 4.8 (range 1–16)
History of tick bite	27 (87.0)
Median days from symptoms to admission (range)	2 days (1–6)
Median days of stay in the hospital (range)	10 days (3–19 days)
Parents with CCHF	5 (16.1)
Families dealing with husbandry	25 (80.6)
Symptoms and signs (%)	
Fever	31 (100)
Malaise	29 (93.5)
Tonsillopharyngitis	23 (74.1)
Nausea-vomiting	21 (67.7)
Headache	14 (45.1)
Diarrhea	12 (38.7)
Myalgia	11 (35.5)
Somnolence	–
Maculopapular rash	5 (16.1)
Hepatomegaly	2 (6.5)
Hemorrhagic symptoms	
Petechia	6 (19.3)
Epistaxis	6 (19.3)
Hematuria	5 (16.1)
Gingival bleeding	4 (12.9)
Melena	3 (9.7)
Hematemesis	2 (6.5)

who had positive IgM and/or positive PCR results for CCHFV in blood or tissue, were included to the study. Virologic studies were performed in Refik Saydam Hygiene Center, which is the national reference laboratory in Ankara, Turkey.

The patients were given erythrocyte, fresh frozen plasma, and total blood preparations depending on their hemostasis. The results of diagnostic studies were not available on the same day due to the present situation of reference laboratory; therefore all of the ribavirin therapy was initiated before the laboratory evidence of CCHF infection. Oral ribavirin was administered within a mean of 5.9 ± 1.9 (3–9) days of onset of symptoms at the dosage recommended by the WHO (30 mg/kg as an initial loading dose, then 15 mg/kg every 6 h for 4 days, and then 7.5 mg/kg every 8 h for 6 days). The total duration of treatment was 10 days.¹⁰ STATA 10 (USA) software package was used in the analysis.

4. Results

During the epidemic period April 2008–October 2009, 31 patients were hospitalized. Twelve (38.7%) of the patients were female, the mean age was 9.4 ± 4.8 (range 1–16) years. The majority of the patients had the history of tick bite (87.0%). Crimean-Congo hemorrhagic fever infection was detected among the parents of 5 (16.1%) children. These five children had the history of tick bite as well. Fever, malaise, nausea-vomiting, diarrhea, tonsillopharyngitis, headache and myalgia were the most common presenting symptoms (Table 1). Among the hemorrhagic symptoms, maculopapular rash, petechia and epistaxis were the most common ones.

Extreme laboratory findings were described in Table 2. The hematological abnormalities were as following: thrombocytopenia (27 cases, 87.0%), leucopenia (26 cases, 83.8%) and bicytopenia (24 cases, 77.4%). Bone marrow aspiration was performed in one patient and revealed haemophagocytosis. Seven children (22.5%) were classified as severe case and 17 (54.8%) children were given ribavirin.

Clinical improvement was observed earlier than the laboratory improvement. Body temperature of the patients were elevated in 2nd day after their hospital admission, lasted for 5 days in average (3–8 days). The mean duration of prehemorrhagic period was 5

Table 2
Laboratory findings.

Characteristics	Mean value (range)
Longest prothrombin time (s)	15.0 (11.2–24)
Longest activated partial thromboplastin time (s)	40.4 (24–95)
Lowest platelet count (platelets/mm ³)	75225 (4000–314.000)
Lowest WBC (WBCs/mm ³)	2353 (730–8800)
Fibrinogen (U/L)	280 (91–379)
Highest lactic dehydrogenase level (U/L)	861 (345–2502)
Highest creatinine phosphokinase level (U/L)	1044 (33–15402)
Highest aspartate transaminase level (U/L)	239 (25–952)
Highest alanine transaminase level (U/L)	123 (23–601)

days (3–9 days). The mean duration for improvement was 6.5 days (4–13 days).

Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio became to the normal levels in average at the 5th day of hospital admission, whereas all other laboratory tests became to normal levels in average after 9 days of hospital admission.

5. Discussion

The CCHF cases in Turkey increased exponentially in recent years. The case fatality rate reported from Ministry of Health of Turkey was 5%.^{11,12} We reported no fatal case among 31 patients, who are under the age of 16. Our data suggest that the disease course is milder among children age group. According to the data held by Ministry of Health of Turkey, there were CCHF confirmed totally 242 cases under eighteen years old in Turkey and 4 deaths were reported in 2008 and 2009 in this age group (CFR: 1.65). Our observations among children age group is contradictory with the findings of a study reported by Mardani et al. from Iran.¹³ In that study the case fatality rate among 34 children was reported as high as 26.5% (9 of 34). In another study from Turkey including 21 children with CCHF, only one fatal case was reported with the fatality rate 4.7%.¹⁴ This fatal case was reported to have severe disease on initial admission, symptoms for the last 2 weeks and multi-system organ failure. He required ventilatory support for pulmonary haemorrhage but did not improve and died during his 3rd week in hospital. The CFR in CCHF infection could be different among different patient populations, because of several reasons. The virulences of different strains, access to the health system, the sensitivity threshold for the symptoms, co-existence of infections, and the last but not the least the host factors could contribute to the different outcomes among the different patient groups.⁹

In previous reports from Turkey including adults, nearly as low as 40–60% of the patients reported the history of tick bites.^{3,4,11} However, in our study, 87.0% of the patients reported the history of tick bite, similar to the previous article from Turkey in 2008 including the same age group like our patients, suggesting 71.4% of positive history of tick bite history.¹⁴ This could be because of the increased public awareness of the problem in recent years.

The time from tick bite to onset of disease was reported as 4 days. In South Africa, the time to onset of disease after exposure to tick bite was 3.2 days, to blood or tissue of livestock was 5 days, and to blood of human cases was 5.6 days. The mean duration of the disease course before the hospital was reported to be 5.5 days in Turkey, and 3.5 days in United Arab Emirates.^{4,15} However in our study, the average time from onset of the disease to admission to the hospital was 2 days.

Clinical improvement was observed earlier than the laboratory improvement. Prothrombin time (PT) and activated partial thromboplastin time (aPTT), and international normalized ratio became to the normal levels in average at the 5th day of hospital admission, whereas all other laboratory tests became

to normal levels in average after 9 days of hospital admission.

Fever, malaise, nausea-vomiting, diarrhea, tonsillopharyngitis, headache and myalgia were the most common presenting symptoms (Table 1). Tonsillopharyngitis and abdominal pain were reported as more common symptoms among the children compared to the adults.^{3,4,16} The proportion of children who had diarrhea was higher than the adult population (20%).¹⁶ Also the rate of myalgia was reported to be more higher comparing to children.^{3,4,16} The mean lower leucocyte values of children in our study were like the adult CCHF patients, while mean lower platelet count in children with CCHF were found to be lower compared to adult studies.^{3,16} The mean days for clinical improvement is seven, whereas the days for laboratory improvement is nine.

Treatment options for CCHF in children are also limited. Supportive therapy is the most essential part of case management and includes intensive monitoring for volume control and administration of platelets, fresh frozen plasma and erythrocyte preparations.^{1,5} Ribavirin is the recommended antiviral agent for patients with CCHF, although its mechanism of action is not clear.¹⁷ In case management, severe cases should be defined and treated.⁴ Severe cases in Turkey are defined according to a revised form of the Swanepoel criteria.^{18–20} It is important to mention that there have been no randomized or controlled studies to confirm the effectiveness of ribavirin against CCHF to date.

Haemolytic anaemia, hypocalcaemia, and hypomagnesaemia were reported in patients treated with ribavirin for severe acute respiratory syndrome.^{21,22} None of these side effects were observed in our patients under ribavirin therapy. Three patients under ribavirin therapy developed sinus bradycardia and returned to normal heart rate after ceasing ribavirin therapy. To our knowledge, sinus bradycardia was not reported before.

In conclusion, the clinical course of CCHF among children seems to be milder than in adults. Tonsillopharyngitis is a common symptom among children with CCHF.

Conflict of interest

The authors declare no conflict of interest.

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