Pediatric cases of Crimean-Congo hemorrhagic fever in Kosovo

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Abstract

Aim: This study represents the epidemiological, clinical and laboratory characteristics of Crimean-Congo Hemorrhagic Fever (CCHF) infection in children.
Methods: In this retrospective study, there were included 27 children infected with CCHF virus. They were treated in the Infectious Diseases Clinic at the University Clinical Center of Kosovo during the time period 2006-2011.
Results: From the 27 children with CCHF, 21 were male (77.8%) and 6 were female (22.2%). Age varied from 16 months to 15 years. The dominating age group was 10-15 years, with a total of 19 cases (70.3%). The majority of children (77.8%) had a history of tick bite. Fever, muscle pain, joint pain, nausea, and vomiting dominated the clinical picture. Increased levels of CPK, LDH, leucopenia and thrombocytopenia were more pronounced in the age group of 10-15 years. CCHF infection was confirmed through ELISA and by real-time polymerase chain reaction (RT-PCR). Ribavirin was given to 51.8% of the cases. Only one case had a fatal outcome. The case fatality ratio was 3.7%.
Conclusion: Crimean-Congo Hemorrhagic Fever is a potentially lethal disease. Milder forms of disease are noted in pediatric patients with CCHF. No significant differences in cytokine level are reported between pediatric patients and adults that could count for less severe forms of CCHF in children. Developing immune system of children may be partly responsible for the differences in the disease course of CCHF observed in this age group.

Keywords: CCHF, children, Kosovo.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral disease. It is caused by the CCHF virus, a member of the genus Nairovirus from the Bunyaviridae family. CCHF is primary a zoonosis, it causes an asymptomatic infection in the affected animals, but once transmitted to humans it can cause a devastating disease with a mortality rate up to 30% (1,2). The CCHF virus is transmitted to humans mainly through tick bites of the Hyalomma genus species and also through direct contact with the excretions, secretions and tissues of infected humans and animals. The Republic of Kosovo is an endemic region for CCHF, with epidemic outbreaks occurring every 4-5 years (3). The first recognized case of CCHF in Kosovo dates back to the year 1954 (3). An authentic strain of CCHF virus from Kosovo, named Kosova Hoti, has been discovered. The complete sequence of its genome revealed that this strain is a highly virulent one (4). CCHF sets as an acute febrile illness with fever, chills, muscle pain, and headache followed by severe hemorrhagic diathesis.

The aim of this study was to describe the epidemiological, clinical and laboratory characteristics of CCHF infection among children in Kosovo.

Methods

This study included 27 children infected with CCHF virus, who were treated in the Infectious Diseases Clinic at the University Clinical Center of Kosovo during the time period 2006-2011. Patients were divided into two groups: group one included patients from 1-9 years old and group two included patients from 10-15 years old. The diagnosis of CCHF was made through epidemiological, clinical and biochemical data and was confirmed by ELISA and RT-PCR.

Results

From the 27 children with CCHF, 21 were male (77.8%) and 6 were female (22.2%). Age varied from 16 months old to 15 years old. The dominating age group was 10-15 years, with a total of 19 cases (70.3%). The admission day after disease onset varied from day 1 of disease to day 7. Based on the geographic distribution, cases from Malisheva, a region in the central part of Kosovo, dominated with a total of 15 cases (56%).

The majority of cases (56%) were hospitalized during the month of June. History of tick bites was present in 21 cases (77.8). Two cases (7.4%) acquired the disease through direct contact. In four cases (14.8%), the history of transmission was unknown. The average incubation period was 3.4 days. Fever was found in 100% of the cases, muscle and joint pain in 77.7% of the cases, nausea and vomiting in 29.6% of the cases, whereas headache was present in 25.9% of the cases (Table 1).

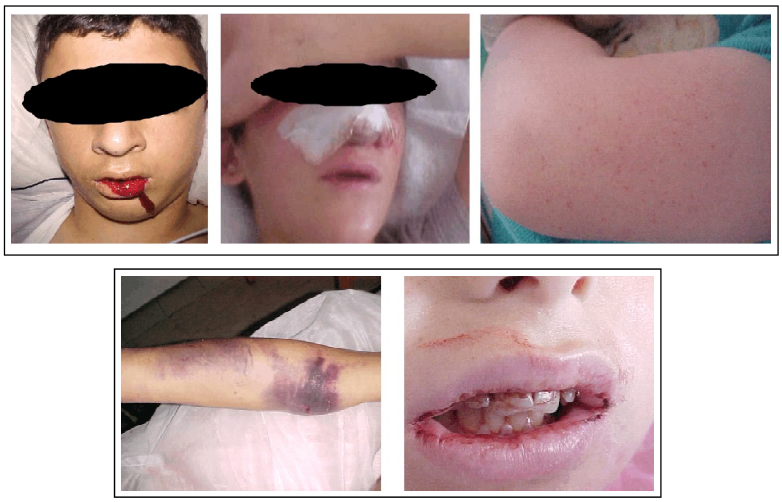
Table 1. Common clinical findings of CCHF in children compared to adults

Symptoms	Children 1-15 y. N (%)	Children 0-9 y. N (%)	Children 10-15 y. N (%)	Adults N (%)
Fever	27 (100)	8 (100)	19 (100)	50 (83.3)
Headache	7 (25.9)	2 (25)	5 (26.3)	38 (63.3)
Muscle and joint pain	21 (77.7)	5 (62.5)	16 (84.2)	57 (95.0)
Fatigue	21 (77.7)	7 (87.5)	14 (73.6)	57 (95.0)
Dizziness	5 (18.5)	2 (25)	3 (15.7)	40 (66.7)
Vomiting	8 (29.6)	3 (37.5)	5 (26.3)	34 (56.6)
Diarrhea	4 (14.8)	2 (25)	2 (10.5)	8 (13.3)

Hemorrhagic syndrome was more prevalent in the age group 10-15 years, with a total of 10 cases (52.6%). Among patients of group two, the most common hemorrhagic manifestations were injected

sclera, epistaxis, subcutaneal hematoma and melena, whereas in group one, bleeding tendency was observed in only two cases in the form of petechiae and injecting sclera. Other hemorrhagic manifestations as gingivorrhagia, vomiting blood, hematoperitoneumi, or hemorrhagic pleuritis were observed only at ages 10-15 years (Figure 1). Jaundice was not observed in any of the children

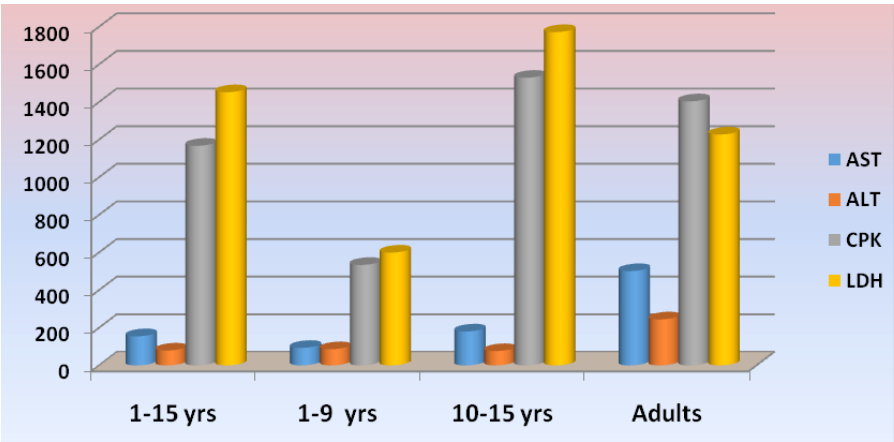
Figure 1. Hemorrhagic manifestation of CCHF in pediatric patients treated at the Infectious Diseases Clinic, UCC Pristina, 2006-2011



with CCHF compared to adult form of CCHF, where liver dysfunction is a common finding.

No marked difference was noted in cardiovascular manifestations in both groups. Central nervous system manifestations are rare findings in children compared to adults. CNS dysfunction was noted in 7.4% of the children in the age group 1-9 years. The alanine (ALT) and aspartate transaminase (AST) level were not markedly increased in children, whereas increased levels of CPK and LDH were noted mostly in the age group of 10-15 years. Upon admission, levels of these enzymes were noted to be as high as AST-818 U/L (normal range >42 U/L); ALT-349 U/L (normal range > 42 U/L); CPK- 3021 U/L (normal range 10 to 120 mcg/L), and LDH- 8067 U/L (normal range 114-240 U/L) [Figure 2].

Figure 2. Levels of liver enzymes, CPK and LDH according to the age groups in children and adults in Kosovo



Leucopenia was present in four patients from group two; the lowest level reported was 1.6 x 10^3/ mm^3 and also in one patient from group 1 with the level being as low as 3.0 x 10^3/mm^3. Thrombocytopenia was found in four patients from group two up to 10×10^9/liter (normal range 140 - 400 × 10^9/litre) and in one patient from group one up to 49×10^9/liter. Anemia was found in recovery phase of disease in five patients, the lowest reported count was 2.9×10^{12} cells/liter (normal range, 4.5 - 5.9 $\times10^{12}$ cells/liter). All cases of CCHF were confirmed through RT-PCR and ELISA. ELISA IgM was positive on day six of the disease, while ELISA IgG was positive by day eleven of disease onset. Treatment with ribavirin was initiated in 14 cases, nine patients received intravenous therapy, whereas five patients received oral therapy. Ribavirin therapy was started on days 3-6 of disease onset. Only one case had a fatal outcome. The case fatality ratio was 3.7%.

Discussion

Crimean-Congo hemorrhagic fever is an acute tick-borne viral disease with cases reported from Africa, Asia and Southeastern Europe (1,2,5,6). Its high mortality rate makes CCHF a potentially lethal disease. Tezer et al. (7) and Ozsurekci (8) characterize the disease by four phases: incubation, prehemorrhagic phase, hemorrhagic phase and convalescence. The incubation period varies according to the mode of transmission and the viral load acquired (5). CCHF sets as a febrile illness with the most reported symptoms being fever, muscle pain, joint pain and headache, followed by mucocutaneous and visceral bleedings. Fatal outcomes usually occur in the hemorrhagic phase due to severe bleeding disorder causing cerebral hemorrhage, anemia, hemorrhagic shock, DIC, multiple organ failure and coma (1,5). Laboratory findings of CCHF consist of anemia, leucopenia, thrombocytopenia, increased levels of AST, ALT, LDH, CPK, increased levels of fibrin degradation products, prolonged prothrombin time (PT) and prolonged activated partial thromboplastin time (aPTT), as well as increased cytokine levels such as TNFα, IL-1, IL-6, and IL-10 (5). Supportive treatment consisting of fluids, transfusion of FFP, erythrocyte and thrombocyte solutions, corticosteroids and antiviral therapy with ribavirin are the mainstays of CCHF treatment (5,6).

CCHF in our pediatric cases was noted to have a milder form. Our pediatric patients with CCHF presented with fever, myalgia, arthralgia and headache, but hemorrhagic manifestations and liver dysfunction were less present compared with findings in adults (5,7,8). Tezer et al. (7) and Ozsurekci et al. (8) also reported similar findings in their studies of pediatric patients with CCHF. The pathophysiology of CCHF is not well-defined, but it is known that there is a complex interplay between viral replication, immune system and vascular endothelium. Ergonul et al. suggested that the massive cytokine release could be responsible for fulminant CCHF disease (9). There were considerations that the differences in cytokine levels in pediatric patients may be responsible for the milder disease course in these patients. However, Oszurekci et al. did not find any significant difference in cytokine levels between pediatric and adult patients (8). There is insufficient data on this matter. To date, the milder form of CCHF in children can only be explained by the immature immune system of children against CCHF virus. Hopefully, in the future, there will be sufficient research that could help explain this phenomenon.

Conclusion

Congo-Crimean hemorrhagic fever is a potentially lethal disease. Milder forms of disease are noted in pediatric patients with CCHF. No significant differences in cytokine levels are reported between pediatric patients and adults that could count for less severe forms of CCHF in children. Development of the immune system of children may be partly responsible for the differences in the disease course of CCHF observed in this age group.

Conflicts of interest: None declared.

References

1. Swanepoel R, Gill DE, Shepherd AJ, Leman PA, Mynhardt JH, Harvey S. The clinical pathology of Crimean–Congo hemorrhagic fever. Rev Infect Dis 1989;11(Suppl.4):S794-800.

2. Whitehouse CA. Crimean–Congohemorrhagic fever. Antiviral Res 2004;64:145–60.

3. Humolli I. Epidemiological and serological characteristics of Crimean-Congo Hemorrhagic Fever in Kosova and determination of CCHF endemic zones in Kosova, 1995-2002. [Dissertation]. University of Pristina, Faculty of Medicine; 2003.

4. Duh D, Nichol ST, Khristova ML, Saksida A, Hafner-Bratkovic I, Petrovec M, Dedushaj I, Ahmeti S, Avsic-Zupanc. The complete genome sequence of a Crimean-Congo Hemorrhagic Fever virus isolated from an endemic region in Kosovo. Virol J 2008;5:7.

5. Duru F, Fisgin T. Hematological aspects of Crimean-Congo hemorrhagic fever. Turk J Hematol 2009;26:161-6.

6. Ahmeti S. Crimean-Congo Hemorrhagic Treatment, in the 5th EuroAsia Congress of Infectious Diseases; 2013 May 15-18; Tirana, Albania; 2013.

7. Tezer H, Sucakli IA, Sayli TR, Celikel E, Yakut I, Kara A, Tunc B, Ergonul O.Crimean-Congo hemorrhagic fever in children. J Clin Virol 2010;48:184–6.

8. Ozsurekci Y, Arasli M, Oncel EK, Caglayik DY, Kaya A, et al. Can the mild clinical course of Crimean–Congo hemorrhagic fever in children be explained by cytokine responses? J Med Virol 2013;85:1955–9.

9. Ergonul O, Tuncbilek S, Baykam N, Celikbas A, Dokuzoguz B. Evaluation of Serum Levels of Interleukin IL–6, IL-10, and Tumor Necrosis Factor–α in Patients with Crimean-Congo Hemorrhagic Fever. J Infect Dis 2006;193:941-4.