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Evaluation of Crimean-Congo Hemorrhagic Fever Virus Infection in Children

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Abstract

Crimean-Congo haemorrhagic fever (CCHF) is a fatal viral infection and an important public health issue in Turkey because of its high case fatality rate. Severity criteria of CCHF were defined previously in adults on the basis of epidemiological, clinical, and laboratory findings,. This study evaluated the course of CCHF in children. Between January, 2009, and November, 2012, 41 patients aged between 1 and 17 years (mean 9.78 ± 4.85) with a diagnosis of CCHF were included in the study. According to results of our study, Turkish pediatric patients had a milder course of CCHF.

Key Words: Crimean–Congo hemorrhagic fever (CCHF)—Mortality—Children.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal fever due to infection with the CCHF virus that has been described in parts of Africa, Asia, eastern Europe, and the Middle East (Burt et al. 1998). CCHF virus is part of the Bunyaviridae family and belongs to the genus *Nairovirus* (Bishop 1996). It causes severe disease in humans, with reported mortality rates of 15–70% Centers for Disease Control and Prevention 1983). Humans become infected through the bites of ticks, by contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viremic livestock Swanepoel et al. 1989). The first case in Turkey was diagnosed in 2002, but by the end of 2006 more than 1100 patients with a confirmed diagnosis by immunoglobulin M (IgM) serology or PCR had been identified, with a fatality rate of 5.4% (Ministry of Health 2007, Vatansever et al. 2007). According to the data held by Ministry of Health of Turkey, there were 734 confirmed cases of CCHF under 18 years old in Turkey, and 14 deaths were reported in 2008 and 2012 in this age group (case fatality rate [CFR] 1.9%). These results suggest that the disease course is milder among children's age group.

Swanepoel et al. (1989) defined the predictors of fatality criteria of CCHF. There are studies analyzing these criteria in adult patients, but studies evaluating the course of CCHF in pediatric patients are not very common. In this study, epidemiological, clinical, and laboratory findings of 41 pediatric CCHF patients were analyzed.

Material and Methods

The study included patients younger than 18 years of age admitted to Ankara Hematology Oncology Children's Training and Research Hospital between January, 2009, and November, 2012, with fever, bleeding, leukopenia, and/or thrombocytopenia with positive IgM and/or PCR results for CCHF in blood. Recent or current CCHF infection was confirmed by demonstrating seroconversion, or at least a four-fold increase in antibody titer in paired serum samples, or IgM antibodies with enzyme-linked immunosorbent assay (ELISA) in a single sample (Charrel et al. 2004). Acute and convalescent sera from all the acute cases were sent to the Refik Saydam Hygiene Center of Ankara, Turkey for ELISA and PCR tests. Physical findings, hematemesis, melena, somnolence, and the laboratory tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], platelets [PLT], white blood cell [WBC] count, lactate dehydrogenase [LDH], creatine phosphokinase [CPK], prothrombin [PT], activated partial thromboplastin time [aPTT], and fibrinogen) were included in data analysis.

Results

Forty-one children (17 female, 41.5%; 24 male) aged between 1 and 17 years of age (mean 9.78 ± 4.85 years) with a diagnosis of CCHF were included in the study. The mean

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hospitalization period was 4.84±2.56 days (min-max 1–10 days). There were no fatal cases. Demographic characteristics of the patients are summarized in Table 1.

By means of laboratory studies for diagnosis of CCHF, 28 patients (68.3%) were PCR positive, 15 patients (%36.6) were IgM positive, and two patients were both IgM and PCR positive. Leukopenia was present in 35 (85.4%) patients, thrombocytopenia in 35 patients, elevated AST, ALT, LDH, and CPK levels in 31, 34 (82.9%), 35 (85.4%), and 20 (48.8%) patients, respectively. Laboratory findings of patients are summarized in Table 2.

On admission 22 patients (53.7%) had elevated aPTT levels and only two patients had a decrease in fibrinogen levels. Oral ribavirin was prescribed for 26 patients (63.4%) and, related to ribavirin therapy, four patients (9.8%) had bradycardia as an adverse event.

Table 1. Demographic Characteristics of 41 Patients with Crimean–Congo Hemorrhagic Fever

Number of females	17(41.5%)
Symptoms	
Nausea-vomiting	23(63.9%)
Myalgia	
Fever	39(95.1%)
Headache	17(41.5%)
Physical findings	
Fever	39(95.1%)
Bleeding	6(16.7%)
Maculopapular rash	5(13.9%)
Conjunctival injection	8(19.5%)
Somnolence	0(0%)
Jaundice	0
Diarrhoea	12(29.3%)
Hepatomegaly	0

Table 2. Laboratory Findings of 41 Patients with Crimean–Congo Hemorrhagic Fever

	Mean (min-max)
Lowest platelet count (platelets/mm^3)	75756 (4000–314,000)
Lowest WBC (WBCs/mm^3)	2138.3 (730–8800)
Highest alanine transferase level (U/L)	132,1 (22–601)
Highest aspartate transferase level (U/L)	248.5 (25–952)
Highest lactic dehydrogenase level (U/L)	873.5 (345–2502)
Highest creatinine phosphokinase level (U/L)	1024.4 (33–15,402)
Lowest fibrinogen level (mg/dL)	264.3 (91–379)
Longest prothrombin time (s)	15.4 (11.2–24)
Longest activated partial thromboplastin time (s)	40.7 (24–95)

Discussion

Owing to lack of randomized clinical trials testing ribavirin, initiation of ribavirin in CCHF patients is a matter of concern. Because severely ill patients need treatment, evaluation of patients by means of clinical and laboratory findings is essential (Ergonul et al. 2004). Swanepoel et al. (1989) defined criteria to evaluate clinical and laboratory findings of CCHF patients, and Ergonul et al. (2006a) revised these parameters according to patients in their study with higher ALT and AST threshold levels (ALT >900 U/L, AST >700 U/L), and they noted that the presence of somnolence, melena, and hematemesis were important additional findings in CCHF patients In a few studies, some prognostic criteria in CCHF are discussed(Bakir et al. 2005, Cevik et al. 2008, Tasdelen Fisgin et al. 2009). Fisgin et al. stated that age is an important criterion in patients with CCHF Burt et al. 1998). Ozturk et al. (2012) defined some additional parameters such as IgA, IgG, C-reactive protein (CRP), D-dimer, C3, and C4. These findings were also present in our patients, but with lower rates: AST levels higher than 150 U/L in 15%, elevated ALT levels higher than 200 U/L in 10%, increased PT levels in 27%, elevated levels of PTT in 54%, decrease in fibrinogen levels in 5%, leukocytosis in 2%, thrombocytopenia in 85%, increase in D-dimer levels in 84%. Because no fatalities were observed in our study, these evaluation parameters defined in adult patients for severity did not match with our patients. The cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were found to be higher among fatal adult CCHF patients compared to nonfatal cases (Ergonul et al. 2006b). Even healthy children have decreased production of cytokines compared to adults (Lilic et al. 1997). A milder course of CCHF in children might be due to lower response of cytokines in pediatric cases. More studies are needed to comment on this subject.

In a study evaluating 50 children with CCHF, similar to our findings, no fatality was observed (Tuygun et al. 2012). Fever was the most common presenting symptom (100%) in a study similar to our study (95.1%). In our study, bradycardia was observed in four patients related to ribavirin; in th Tuygun et al. study, no adverse events were observed related to ribavirin, although 23 patients (46%) were given ribavirin.

The use of ribavirin in treatment of CCHF is controversial. In a study analyzing the use of ribavirin fatality rates was essentially the same in treated and untreated cases (Ergonul et al. 2006), yet in another study, ribavirin did not have any significant difference on fatality rates or on the need for blood and blood products, in the mean duration of hospitalization or hospital expenditure values (Ozkurt et al. 2006). In our study, 26 patients (63.4%) were prescribed ribavirin and it did not affect outcome in the patients.

The outcome of CCHF in children was reported to be milder in the literature, with mortality rates ranging between 0% and 4.7% (Dilber et al. 2009, Texer et al. 2010, Tuygun et al. 2012). Our study complies with this finding showing additionally that adult patients have a more severe course of CCHF compared to pediatric patients. A milder course of CCHF in a pediatric population might be due to the varying virulences of different strains, early access of children to the health system, and also the host factors (Tezer et al. 2010). Further studies are needed to evaluate the reasons of milder course of pediatric cases.

Author Disclosure Statement

No competing financial interests exist.

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