



Original article

Transient sinus bradycardia during the course of Crimean-Congo hemorrhagic fever in children



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ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF) is an acute tick-borne viral zoonotic disease which is endemic in Turkey. Bradycardia has been reported among pediatric and adult patients with CCHF. But, it remains unclear, whether bradycardia is associated with ribavirin treatment or the severity of CCHF. In this study 26 hospitalized CCHF patients were reviewed in terms of age, gender, history of tick bite, duration of hospitalization, presence of bradycardia, laboratory features, ribavirin treatment, and blood products requirement. The demographic, clinical, laboratory and treatment characteristics of CCHF patients with or without bradycardia were compared. The mean age of the patients was 126.42 ± 48.21 months. There were 8 female and 18 male patients. Sinus bradycardia was noted in 15 patients (mean age was 120.20 ± 50.59 months, 5 female). Ribavirin had been administered 18 (69.2%) patients and 11 of them had bradycardia. There was not statistically significant relationships between bradycardia and ribavirin treatment ($p = 0.683$). Furthermore the occurrence of bradycardia was not associated with disease severity according to Swanepoel severity criteria ($p = 0.683$). We concluded that independent of the disease severity and the ribavirin treatment, transient sinus bradycardia might occur during the clinical course of CCHF in pediatric patients. For this reason clinicians should be aware of this finding and all CCHF patients should be monitored closely.

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Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute tick-borne viral zoonosis transmitted to humans by Hyalomma ticks or via direct contact with the blood of infected humans or domestic animals. Crimean-Congo hemorrhagic fever virus (CCHFV) belongs to the *Nairovirus* genus of the *Bunyaviridae* family. The disease is widely distributed more than 30 countries, including Turkey. Currently, CCHF is an endemic disease in Turkey has been since 2002. According to the Turkish Ministry of Health, there were 7192

reported cases with a mortality rate of 5% (unpublished data). It was reported that the course of the disease is less severe in children than in adults in Turkey, and that the mortality rate is 0–1.9% (Ofilaz et al., 2013; Tuygun et al., 2012). The clinical characteristics of patients with CCHF vary widely in disease severity from mild to fatal outcome (Ergonul et al., 2006).

Relative bradycardia is among the non-specific prodromal symptoms of the pre-hemorrhagic phase of CCHF that include high fever, myalgia, headache, nausea, abdominal pain, non-bloody diarrhea, tachypnea, conjunctivitis, pharyngitis, and cutaneous flushing or rash (Mardani and Keshtkar-Jahromi, 2007). Relative bradycardia is a heart rate that is too slow for those with a body temperature $>38.3^\circ\text{C}$. Although relative bradycardia is a well-known clinical entity in such infections as typhoid fever, typhus, Rocky Mountain spotted fever, Legionnaire's disease, psittacosis, sand fly fever, dengue fever, yellow fever, viral hemorrhagic fever, leptospirosis, malaria, and babesiosis, absolute sinus bradycardia during an infectious disease is rare, but can occur in patients with such infections as viral hepatitis A, hemorrhagic fever with renal syndrome, and leptospirosis (Erol et al., 2012). Sinus bradycardia, is reported in

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both adult and pediatric CCHF patients with increasing frequency (Ofiaz et al., 2013; Erol et al., 2012; Uysal and Metan, 2012). It remains unclear, however, if bradycardia is associated with ribavirin treatment or the severity of CCHF. The present study aimed to determine the clinical and laboratory characteristics of pediatric CCHF patients with and without bradycardia, the relationship between bradycardia and ribavirin treatment, and the relationship between bradycardia and disease severity.

Materials and methods

In total, confirmed 58 CCHF patients aged <18 years were followed at Dr. Sami Ulus Maternity and Children's Research and Education Hospital, Ankara, between 2005 and 2013. Acute and convalescent phase serum samples were sent to Refik Saydam National Public Health Agency (RSNPHA), Virology Reference and Research Laboratory, Ankara, Turkey, for microbiological testing for CCHFV infection. CCHFV infection was definitively diagnosed based on detection of CCHFV-specific IgM antibodies via enzyme-linked immunosorbent assay (ELISA) or genomic segments of the CCHFV via reverse transcription polymerase chain reaction (RT-PCR) in the serum samples of patients with typical clinical and epidemiological findings. Nursery observation cards that included hourly vital signs and ECG findings were available for only 26 of the 58 patients. For this reason these 26 patients were included in the present study focused on the association with CCHF and bradycardia.

All suspected CCHF patients were hospitalized and isolated, and barrier nursing was implemented to prevent nosocomial transmission. All patients were given general supportive management, including monitoring of vital signs, replacement of fluid and electrolytes, and administration of platelet suspension, fresh frozen plasma and erythrocyte suspension, as needed. Oral ribavirin was given to the patients with severe disease and/or bleeding symptoms, at the dosage recommended by the World Health Organization (WHO) (30 mg/kg as an initial loading dose, followed by 15 mg/kg every 6 h for 4 days, and then 7.5 mg/kg every 8 h for 6 days) (WHO, 2009).

The age, gender, history of tick bite, duration of hospitalization, presence of bradycardia, laboratory features, ribavirin therapy, and blood products requirement were recorded. Bradycardia was defined as a heart rate 2 standard deviations (SDs) lower than the expected heart rate based on age. Electrocardiography (ECG) findings were obtained for all the patients with bradycardia. The hemoglobin (Hb) level, peripheral blood leukocyte count, platelet count, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), activated partial thromboplastin time (aPTT), C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) were recorded for each patient. Complete blood count and biochemical laboratory parameters were evaluated daily, or according to patient need. All CCHF patients were classified into two groups in terms of disease severity as 'severe' and 'non-severe', according to the predictive factors for fatal outcome reported by Swanepoel and co-workers. These severity criteria of CCHF included platelet count (<20,000/mm³) and/or aPTT (>60 s), and/or leukocyte count (>10,000/mm³) and/or fibrinogen (<110 mg/dL) and/or elevated AST and ALT levels (Swanepoel et al., 1989). Finally, the demographic, clinical, laboratory and treatment characteristics and disease severity of CCHF patients with or without bradycardia were compared.

Statistical analyses were performed by using "SPSS for Windows version 15.0". Normally distributed data were expressed as mean ± standard deviation; nonnormally distributed data were expressed as median and interquartile range; categorical variables were reported as percentages (%). Shapiro–Wilk test was used to test the normality of continuous variables (AST, ALT, PT, PTT). For

non-normally distributed data, comparison was performed using Mann–Whitney *U* test; comparison of normally distributed data was performed using independent-samples *t* test. Qualitative data were compared by Pearson Chi-square and Fisher exact test. Statistical significance level for all tests was accepted as *p* < 0.05.

Results

In all, 8 (30.7%) of the patients were female, 18 (69.2%) were male, and mean age was 126.42 ± 48.21 months (range: 30–200 months). History of tick bite was positive in 19 (73%) patients. Patients with CCHF presented most commonly during July and August. Among the patients, 23 (88.5%) had leukopenia and 13 (50%) had thrombocytopenia during the disease course. In all, 22 (84.61%) of the 26 patients had an elevated AST, 19 (73.07%) had an elevated ALT, and 10 (38.4%) had a prolonged PT and 19 (73.07%) had a prolonged aPTT at admission. Ribavirin was administered to 18 (69.2%) patients. Blood products were required in 20 (76.9%) patients. Mean duration of hospital was 10 days (range: 5.0–15.0 days). None of the 26 patients died. Characteristics of the CCHF patients are shown in Table 1.

Bradycardia was noted in 15 (57.7%) of the 26 patients during clinical follow-up; 10 (66.6%) of the patients with bradycardia were male, 5 (33.3%) were female, and mean age was 120.20 ± 50.59 months (range: 30 months–200 months). The distribution of the mean value of heart rates of patients with or without bradycardia based on the days was demonstrated in Fig. 1. In all, 14 (93.3%) of the 15 patients with bradycardia had an elevated AST, 11 (73.3%) had an elevated ALT, 8 (53.3%) had a prolonged PT, and 13 (86.7%) had a prolonged aPTT at admission. Electrocardiographic examination showed that all 15 patients with bradycardia had sinus bradycardia. Bradycardia was observed at a mean 2.87 ± 1.35 day (median 3, range 1–6 days) of hospitalization. In all, 11 (61.1%) of the 15 patients with bradycardia were receiving ribavirin treatment. Bradycardia resolved at a mean of 7.7 ± 3.0 days (median 8, range 3–12 days) of hospitalization. There was not statistically significant relationship between bradycardia and ribavirin treatment (*p* = 0.683). According to Swanepoel severity criteria, 9 (34, 6%) of the 26 patients were classified as severe disease and 17 (65.38%) as non-severe. In the respect of Swanepoel

Table 1
Characteristics of the CCHF patients.

Parameters	
Age (months), mean ± SD	126.42 ± 48.21
Sex, n (%)	
Female	8 (30.7%)
Male	18 (69.2%)
History of tick bite	19 (73%)
Days of stay in hospital	10 (5–15)
Presence of bradycardia	15 (57.6%)
Onset of bradycardia time	3 (1–6)
Laboratory features	
Thrombocytopenia (%) ^a	13 (50%)
Leukopenia (%) ^b	23 (88.5%)
Sedimentation rate (mm/h)	15 (3–110)
CRP	9.25 (1–240)
Impairment in liver function tests (elevated AST/ALT) (%)	19 (73.1%)
Bleeding disorder (prolonged PT/aPTT) (%)	7 (26.9%)
Ribavirin therapy (%)	18 (69.2%)
Need for blood product (%)	20 (76.9%)
Severe clinical form	9 (34.6%)
Death	0

CCHF, Crimean-Congo hemorrhagic fever; CRP, c-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; PT, prothrombin time; aPTT, activated partial thromboplastin time.

^a Thrombocytopenia = platelet count < 150,000/mm.

^b Leukopenia = leukocyte count < 4000/mm.

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