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Transient bradycardia in patients with Crimean-Congo hemorrhagic fever

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Aim: To determine the features and clinical course of bradycardia in patients with Crimean-Congo hemorrhagic fever (CCHF).

Materials and methods: Between May 2002 and September 2010, a total of 380 patients with CCHF were followed. All patients who had transient bradycardia during this period were included in the study.

Results: A total of 14 patients had an episode of bradycardia. All patients were in sinus rhythm. Three patients had clinical symptoms of bradycardia; atropine was administered to them. In the other patients, bradycardia resolved spontaneously. No patient had underlying conditions for bradycardia. Bradycardia appeared 7.0 ± 1.7 days after the first clinical symptoms, continued for 5.1 ± 1.6 days, and resolved without any additional problems.

Conclusion: Transient sinus bradycardia is a rare and benign clinical manifestation of CCHF. In many cases, there is no need for intervention.

Key words: Crimean-Congo hemorrhagic fever, bradycardia

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic disease caused by the CCHF virus (CCHFV), which belongs to the genus *Nairovirus* of the family *Bunyaviridae*. The CCHFV is enzootic in the southern part of Europe (Balkans), Turkey, the southern Russian Federation, several countries in the Middle East, sub-Saharan Africa, central Asia, and the western part of China (1-4). CCHF virus is transmitted to humans primarily by bites of infected ticks (5).

Except for newborn mice, humans appear to be the only CCHFV host in which the disease is manifested. There are a variety of potential clinical manifestations following infection with this virus, and not all patients develop the classic form of the disease. The typical course of CCHF has been noted by some authors as progressing through 4 distinct phases: incubation, prehemorrhagic, hemorrhagic, and convalescence. However, the duration and associated symptoms of these phases can vary greatly. Patients initially exhibit a nonspecific prodrome, which typically lasts less than 1 week. Clinical manifestations are nonspecific and may include high fever, headache, malaise, arthralgia, myalgia, nausea, abdominal pain, nonbloody diarrhea, and hypotension. In severe cases, 3-6 days after the onset of disease, hemorrhagic manifestations develop (1,2,6). Patients may show signs of progressive hemorrhagic diathesis such as petechiae, mucous membrane and conjunctival hemorrhage, hematuria, hematemesis, and melena. Disseminated intravascular coagulation (DIC) and shock may ensue. Relative bradycardia, hypotension, tachypnea, abdominal tenderness, watery diarrhea, icterus, and lethargy are less prevalent signs in the

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course of CCHF. Although some cardiovascular changes, e.g., bradycardia and low blood pressure, were emphasized in earlier publications (1,7,8), these have not been reported in recent studies (2,9-12). In addition, to our knowledge, there is no study detailing bradycardia in this patient group.

The main objective of this study was to determine the frequency and clinical course of bradycardia in patients with CCHF.

Material and methods

Between May 2002 and September 2010, a total of 380 patients with CCHF, 215 male (56.6%) and 165 female (43.4%), were followed at the Department of Infectious Diseases and Clinical Microbiology of Atatürk University's Faculty of Medicine. All patients who had a transient bradycardia episode during this period were included in the study. In the presence of suggestive clinical findings, diagnosis of CCHF was confirmed by the positivity of CCHFV-specific IgM antibody or detection of CCHFV RNA by polymerase chain reaction (PCR) in blood samples of the patients (13). All CCHF patients who had cardiovascular symptoms or signs were examined by a cardiologist and were investigated by electrocardiogram and, in some cases, echocardiography.

Bradycardia (sinus bradycardia or absolute bradycardia) was defined as a heart rate of less than 60 beats/min (14). In this case, the rhythm is usually regular; the P waves are identical, normal, and constant; and each P wave precedes a QRS complex, which is usually of normal width.

Results

During the study period, 14 of the 380 patients had an episode of bradycardia. All patients were in sinus rhythm according to electrocardiograms. The characteristics of the bradycardiac patients are listed in the Table. Three patients had clinical symptoms of bradycardia (dizziness, shortness of breath, and hypotension) and intravenous atropine was administered to them. The patients were responsive to atropine. In the other patients, the episodes were not associated with signs of hemodynamic instability, and bradycardia resolved spontaneously. No patients, except one, had underlying conditions for bradycardia such as electrolyte disorder, drug use, toxic exposure, hypoglycemia, hypothyroidism, previous cardiac

Table. Characteristics of the patients.

Characteristic	Mean (range)
Age, years	46.2 ± 19.8 (18-76)
Sex (female/male)	3/11
Previous cardiac disorder or other underlying conditions	1
Onset of the bradycardia (days from first clinical symptoms)	7 ± 1.7 (5-10)
Duration of bradycardia (days)	5. 1 ± 1.6 (2-8)
Lowest WBC* count/mm^3	1785 ± 683 (800-3500)
Lowest platelet count/mm^3	47,785 ± 25,917 (12,000-97,000)
Highest total bilirubin level, mg/dL	0.92 ± 0.90 (0.3-3.60)
Highest ALT level, IU/L**	239.1 ± 205.3(31-612)

*White blood cells
**Alanine aminotransferase

disorder, or increased intracranial pressure. Only one patient had right atrial dilatation by echocardiogram. Of the 14 patients, 3 received oral ribavirin treatment. Among these, only one patient was under ribavirin treatment during the bradycardia episode. In the 2 other patients, bradycardia occurred before ribavirin use or after the cessation of the drug.

Although the majority of the bradycardiac patients were male (78.6%), the male-to-female ratio was similar when compared to the total CCHF patient group (3/11 vs. 165/215; P = 0.17 by chi-square test)

The mean duration of bradycardia was 5.1 ± 1.6 days (range: 2-8) and the bradycardia resolved without any additional problem or sequelae. All patients had a good prognosis for CCHF with full recovery and 1-month survival after discharge from hospital.

Discussion

There are 2 types of bradycardia: absolute and relative. Absolute bradycardia refers to any heart rate below 60 beats/min (14). The term "relative bradycardia" is used to explain a heart rate that, while not technically below 60 beats/min, is considered to be too slow for the individual's current medical condition, especially in pulse-temperature discrepancy when the temperature exceeds 38.3 °C. Relative bradycardia is a well-known clinical entity in infections and is caused by gram-negative intracellular organisms such as those in typhoid fever, typhus, Rocky Mountain spotted fever, Legionnaire's disease, and psittacosis; however, it is not limited to these. It is also associated with sand fly fever, dengue fever, yellow fever, viral hemorrhagic fever, and leptospirosis. Furthermore, the protozoal parasites of malaria and babesiosis are also associated with relative bradycardia (15). In contrast, absolute sinus bradycardia during infectious diseases is a rare condition. It has been reported that bradycardia and sinus node dysfunction may be seen in some viral and bacterial infections such as viral hepatitis A, hemorrhagic fever with renal syndrome, and leptospirosis (16-19).

CCHF is a multisystemic disease. Although cardiovascular changes in CCHF are not always present, some cardiovascular involvement was emphasized in a few previous publications (1,7,8,10,20). In our previous study, the cardiovascular involvement rate was 7.6% (10). Among cardiovascular findings, bradycardia was emphasized in a few studies (3,7,21).

In a recent study from Turkey, Engin et al. investigated cardiac involvement in patients with CCHF. Although they reported impaired cardiac function, especially in severe cases, bradycardia was not mentioned (20). Tezer et al. reported 3 children who presented with bradycardia under ribavirin treatment. They reported that bradycardia resolved after the ribavirin treatment was ceased (21). The authors attributed bradycardia to ribavirin use in their patient group. Bradycardia was not related to ribavirin use in our cases. No patients, except one, were under ribavirin treatment when bradycardia occurred.

It has been shown previously in experimental and clinical studies that hemorrhagic fever viruses are able to cause cardiac involvement (22,23). Cardiac congestion and edema in the heart tissues has been reported in fatal cases of CCHF (24). Depressed left ventricular ejection fraction, higher systolic pulmonary artery pressure, and pericardial effusion were also reported in severe cases in a recent study (20). The specific underlying mechanisms for cardiovascular involvement are not well understood in CCHF. Direct invasion of the heart muscles by the virus or endothelial damage of cardiac structures may play a role. Previous experimental studies have shown that Toll-like receptor 2 (TLR2)-mediated signaling in the heart is associated with increased tumor necrosis factor (TNF), interleukin-1β, and nitric oxide expression (25). Interleukin-1 and TNF-α have arrhythmogenic effects in cultured cardiomyocytes, whereas their overexpression within the perisinoatrial nodal area has been related to the weakness of the sinoatrial node dominance of the heart and may impair the normal transmission of the impulse from the sinoatrial node to the rest of the heart (26). The role of TLRs, TNF-α, and interleukins in CCHF were shown in some studies (27-30). TLRs and cytokines may have a role in the occurrence of bradycardia in patients with CCHF. Further studies are required to explain the exact mechanism of bradycardia.

The study suggests that transient sinus bradycardia is a rare and benign clinical manifestation of CCHF. This is the first study to detail bradycardia in this patient population.

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