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Crimean-Congo hemorrhagic fever: does it involve the heart?

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Summary
Objective: Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic fever with a high mortality rate. Despite increasing knowledge about viral hemorrhagic fevers, the pathogenesis of CCHF and causes of death have not been well described. In this study, we aimed to evaluate the cardiac functions of CCHF patients.
Methods: This prospective study was performed among confirmed CCHF cases in Turkey in 2007. All the patients underwent a thorough cardiologic evaluation and transthoracic echocardiography examination within 24 hours of hospitalization. In addition, the patients were classified into two groups — 'severe' CCHF and 'non-severe' CCHF. Demographic characteristics, findings of echocardiography, and outcomes were recorded for each patient.
Results: Among 52 consecutive patients with a tentative diagnosis of CCHF, 44 were confirmed as having CCHF. Seventeen (38.6%) patients were classified as severe, whereas the remaining 27 (61.4%) patients were classified as non-severe. Five of 17 severe CCHF patients died. Severe cases had a lower left ventricular ejection fraction ($p = 0.04$), a higher systolic pulmonary artery pressure ($p = 0.02$), and more frequent pericardial effusion ($p < 0.001$) compared to non-severe cases. Fatal CCHF cases also had a lower left ventricular ejection fraction ($p = 0.03$), a higher systolic pulmonary artery pressure ($p = 0.03$), and more frequent pericardial effusion ($p = 0.01$) compared to survivors.
Conclusions: The results of this study indicate that severe and fatal CCHF cases have impaired cardiac functions, which may be associated with fatality in CCHF infection. Direct invasion of the heart muscles by the virus or endothelial damage of cardiac structures may have a role in this.

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Molecular testing methods would be useful in order to investigate direct invasion by the CCHF virus. Clinicians should be aware of this complication.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic fever (VHF) with a case fatality rate of 10–30%. It is caused by infection with the CCHF virus, which belongs to the genus *Nairovirus* of the family *Bunyaviridae*. CCHF was first described in the 1940s, when more than 200 human cases occurred in the Crimean peninsula of the former Soviet Union, and it is now endemic in many different regions of Africa, Asia, and Eastern Europe. Human beings become infected through tick bites, by crushing infected ticks, after contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viremic livestock. The most important clinical features are fever and in the most severe cases, shock and hemorrhage. Despite increasing knowledge about hemorrhagic fever viruses, the pathogenesis of CCHF and causes of death have not been well described.[1,2] It has been reported that mononuclear phagocytes, hepatocytes, and endothelial cells are major targets of CCHF virus infection.[3] However, to our knowledge, the data available on the cellular targets and distribution of CCHF virus in human tissues remain limited.

Fatal illness in VHF is characterized by rapid development of refractory shock, severe coagulopathy, and multifocal necrosis of the liver and other viscera.[4] Factors contributing to a fatal outcome for CCHF are reported to include severe gastrointestinal hemorrhage, cerebral hemorrhage, severe anemia and dehydration, and shock associated with prolonged diarrhea, myocardial infarction, lung edema, and pleural effusion.[5–9] However, several viral agents are known to cause myocarditis and cardiomyopathy including hemorrhagic fever viruses.[10–15] Cardiac involvement may have a contributing role in the pathogenesis of shock in CCHF and may also influence the outcome. To our knowledge, the literature presents no echocardiographic studies on cardiac involvement in patients with CCHF. This study was therefore undertaken to elucidate data on cardiac involvement in CCHF patients.

Materials and methods

After obtaining approval from the Human Ethics Committee of Cumhuriyet University School of Medicine, 52 consecutive patients who were hospitalized with a tentative diagnosis of CCHF between June 1 and June 30, 2007 were enrolled in our study. Informed consent was also obtained from the patients. As per the protocol, all patients underwent a thorough cardiologic evaluation by a cardiologist after hospitalization. Following this, within 24 hours of hospitalization, all patients underwent a transthoracic echocardiography examination using an appropriate probe (Sonosite Inc., Bothell, WA, USA); this was carried out by an echocardiographer who was blinded to the study. The same echocardiographer measured the ventricular (by modified Simpson method) and valvular functions, wall motion scores, presence of pericardial effusion, pulmonary pressures, diastolic functions by measuring early diastolic mitral velocity (E wave) and late diastolic mitral velocity (A wave), and the E/A ratio (normal E/A ratio: 1–2) according to the recommendations of recent guidelines.[16] Electrocardiography (ECG) recordings were obtained from all the patients. All the echocardiographic data were recorded and evaluated offline by an experienced cardiologist.

CCHF infection was suspected if a patient had an epidemiologic risk factor (history of tick exposure and/or resident in or traveled to a CCHF endemic region) plus an acute febrile illness resembling VHF (oral temperature $>38\ ^{\circ}C$) and thrombocytopenia (platelet count $<150 \times 10^9$ cells/l) and/or hemorrhagic manifestations. These patients were hospitalized immediately, and serum samples were obtained from all for diagnostic studies. A convalescent phase serum sample was obtained from each patient after at least 7 days when possible. Acute and convalescent phase serum samples were sent to the Virology Laboratory of Refik Saydam Hygiene Central Institute, Ankara, Turkey for serologic and virologic analyses. The definitive diagnosis of CCHF infection was based upon typical clinical and epidemiological findings and detection of CCHF virus-specific IgM by ELISA or of genomic segments of the CCHF virus by reverse transcription-polymerase chain reaction (RT-PCR) either in the acute and/or convalescent phase of the disease. In the study, all confirmed CCHF patients were classified into two groups in terms of disease severity ('severe' and 'non-severe'), according to the predictive factors for fatal outcome reported by Swanepoel and co-workers.[5]

Patients with pathological Q waves in their initial ECG, patients with a previous history of cardiac disease, including significant left-sided valvular disease, and patients using anticoagulant drugs were not included in the study. All the patients received appropriate therapy including supportive care with intravenous fluids and platelet suspension, and blood and fresh frozen plasma transfusion, when indicated.

Statistical analysis

The demographic characteristics and echocardiography findings were recorded for each patient. The parametric data were expressed as mean $\pm$ SD and categorical data as percentages. Independent parameters were compared by Mann–Whitney U-test. Proportions for categorical variables were compared using the Chi-square test, although Fisher's exact test was used when the data were sparse. A p value of ≤ 0.05 was considered significant, using two-sided comparisons. SPSS (version 10.0) was used to perform statistical procedures.

Results

In this study, the diagnoses of 44 out of 52 consecutive patients with a tentative diagnosis of CCHF were verified. Twelve (27.3%) of 44 patients had CCHF virus-specific IgM antibodies, 2/44 (4.5%) had a positive RT-PCR test for CCHF

Table 1 Comparison of the demographic characteristics and echocardiography findings of the severe and non-severe Crimean-Congo hemorrhagic fever (CCHF) patients.

Variable	Severe CCHF (n = 17)	Non-severe CCHF (n = 27)	p-Value
Age (years), mean ± SD	41.9 ± 22.7	47.7 ± 21.7	0.41
Female gender, n (%)	7 (41.2)	16 (59.3)	0.39
Hospitalization days, mean ± SD	9.3 ± 2.9	6.5 ± 2.5	0.01
Fatal outcome, n (%)	5 (29.4)	0	0.01
Echocardiography findings:			
Percent ejection fraction, mean ± SD	50 ± 7	55 ± 9	0.04
Systolic pulmonary artery pressure (mmHg), mean ± SD	48 ± 6	36 ± 10	0.02
Pericardial effusion, n (%)	13 (76.5)	6 (22.2)	<0.001
Tricuspid regurgitation, n (%)	9 (52.9)	8 (29.6)	0.22
Global wall motion abnormality, n (%)	2 (11.8)	1 (3.7)	0.55
Wall motion abnormality on anterior wall, n (%)	3 (17.6)	2 (7.4)	0.36
Abnormal diastolic function up on abnormal E/A ratio,[a] n (%)	14 (82.4)	15 (55.6)	0.10

[a] E/A, early diastolic mitral velocity (E wave)/late diastolic mitral velocity (A wave).

virus, and 30/44 (68.2%) were positive in both tests during the acute and/or convalescent phase of the disease. According to the severity score,[5] as defined previously, 17 (38.6%) patients were classified as severe, whereas the remaining 27 (61.4%) patients were classified as non-severe. Of the 44 consecutive patients with CCHF, five (11.4%) of them died during the hospitalization period.

Table 1 shows the demographic characteristics and echocardiography findings of the severe and non-severe CCHF patients. Severe CCHF patients had a significantly lower ejection fraction (EF) than non-severe CCHF patients (50% vs. 55%; $p = 0.04$) based on the echocardiographic examination, and a significantly higher systolic pulmonary artery pressure ($p = 0.02$) than non-severe CCHF patients. There was a significant association between severity and the presence of pericardial effusion ($p < 0.001$). Severity was also associated with survival; five of 17 (29.4%) patients with severe CCHF died, whereas none of the patients with non-severe CCHF died ($p = 0.01$).

Table 2 presents the demographic characteristics and echocardiography findings of the fatal and non-fatal CCHF patients. In the patients with fatal CCHF, the mean EF was significantly lower, whereas the mean systolic pulmonary artery pressure was significantly higher than in those with non-fatal CCHF ($p = 0.03$). Although all of the fatal CCHF patients had varying degrees of pericardial effusion, 35.9% of non-fatal CCHF patients had pericardial effusion ($p = 0.01$). When EF was subclassified into depressed EF (<50%) or normal EF (≥50%), it was found that four out of five fatal CCHF patients had depressed EF, while 25.6% of the non-fatal CCHF patients had depressed EF ($p = 0.03$).

Discussion

To date, the specific mechanisms underlying the pathogenesis of CCHF infection have not been clearly explained.[1,2,17] The severe form of CCHF is characterized by hemorrhage,

Table 2 Comparison of the demographic characteristics and echocardiography findings of the fatal and non-fatal Crimean-Congo hemorrhagic fever (CCHF) patients.

Variable	Fatal CCHF (n = 5)	Non-fatal CCHF (n = 39)	p-Value
Age (years), mean ± SD	50.4 ± 23.6	44.8 ± 22.1	0.62
Female gender, n (%)	3 (60)	20 (51.3)	1.00
Echocardiography findings:			
Percent ejection fraction, mean ± SD	45 ± 9	54 ± 8	0.03
Systolic pulmonary artery pressure (mmHg), mean ± SD	50 ± 6	39 ± 9	0.03
Pericardial effusion, n (%)	5 (100)	14 (35.9)	0.01
Tricuspid regurgitation, n (%)	4 (80)	13 (33.3)	0.07
Global wall motion abnormality, n (%)	2 (40)	1 (2.6)	0.03
Wall motion abnormality on anterior wall, n (%)	3 (60)	2 (5.1)	0.01
Abnormal diastolic function up on abnormal E/A ratio,[a] n (%)	5 (100)	24 (61.5)	0.15

[a] E/A, early diastolic mitral velocity (E wave)/late diastolic mitral velocity (A wave).

disseminated intravascular coagulation, vascular dysfunction, and shock.[1,6–8] Mononuclear phagocytes, hepatocytes, and endothelial cells are major targets for the CCHF virus during the course of the infection.[3] In particular, infection of the endothelium has an important role in CCHF pathogenesis. Endothelial damage contributes to hemostatic failure by stimulating platelet aggregation and degranulation, with consequent activation of the intrinsic coagulation cascade.[2–9] In VHFs, impairment of endothelial cell function can cause a wide range of vascular effects that lead to changes in vascular permeability or hemorrhage.[17] Increased vascular permeability leads to the hypovolemic shock in dengue shock syndrome (DSS) by leakage of water, proteins, and electrolytes from the vascular compartment.[11] On the other hand, it is probable that the endothelium plays a role in the pathogenesis of VHF through the secretion of cytokines and other inflammatory mediators.[3] Recently, the serum levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6 were found to be higher in fatal than non-fatal CCHF cases.[18]

The most comprehensive study of the clinical pathology of CCHF is that of Swanepoel et al.,[5] in which observations were made on 50 CCHF patients in South Africa diagnosed between 1981 and 1987. Of the 50 patients studied, 15 patients who died had developed terminal multiple organ failure and pulmonary insufficiency. Another histopathological study showed hepatocellular necrosis in all and splenic lymphoid depletion and necrosis in 11 of 12 fatal CCHF cases. In that study, congestion and interstitial edema in the heart tissues of one fatal CCHF case were also shown.[3] The observation of cardiac congestion and edema in that fatal CCHF case may support cardiac involvement. However, little is known about the effect of CCHF virus on the heart.

Although myocarditis and cardiomyopathy can be caused by several different viruses, the Coxsackie A and B viruses and adenovirus are the most frequent agents amongst them.[10,14] Both immune and direct viral cytotoxic mechanisms of myocardial tissue destruction are important in the pathogenesis of viral myocarditis. Natural killer cells, T lymphocytes, and various cytokines, including interleukin (IL)-1β, TNF-α, interferon-γ, and IL-10 may have both beneficial and deleterious effects on myocardial function. The direct effects of virus-mediated cytotoxicity include focal necrosis of myocytes without inflammatory cell infiltrate.[14] It has been shown previously in experimental and clinical studies that hemorrhagic fever viruses are also able to cause cardiac involvement. Histologic myocardial lesions, including focal lymphoblastic infiltrates, vascular ruptures, and mild interstitial reactive change demonstrating cardiac involvement have been observed in experimental Junin virus-infected monkeys.[13] Dengue virus and yellow fever virus, members of the *Flavivirus* genus of the *Flaviviridae* family, can also cause cardiac involvement in humans.[10,11,15,19] Hantavirus belonging to the *Bunyaviridae* family, the same family as that of the CCHF virus, causes hantavirus pulmonary syndrome (HPS). Recently, it has been reported that the presence of hantaviral antigen in the cardiac endothelium and interstitial macrophages in the hearts of 14 individuals who died of HPS strongly suggests typical myocarditis in HPS.[12] Molecular testing of heart muscle endothelium for the presence of CCHF virus by RT-PCR, and culture of the heart tissues would be useful in order to investigate direct invasion by CCHF virus. However, myocardial biopsy could be fatal due to the low platelet count in CCHF patients.

Echocardiography may be helpful but is not diagnostic in viral myocardial involvement.[10,14,20] Left ventricular systolic dysfunction reflecting a myocarditic process is common in patients with congestive heart failure. Additional findings are right ventricular dysfunction, hypo-asynergic ventricular areas, left ventricular hypertrophy, hyper-refractile myocardial areas, ventricular thrombi, and restrictive ventricular filling.[20] In the present study, CCHF patients had a considerable amount of cardiac involvement.

In this study group, EF was significantly more depressed in the severe CCHF group compared to the non-severe CCHF group. It was also significantly more depressed in the fatal CCHF patients than in the non-fatal CCHF patients. In addition to this, the severe and the fatal CCHF patients had more frequent involvement of the pericardium and right ventricle than the non-severe and non-fatal CCHF patients. The echocardiography findings of 17 dengue hemorrhagic fever (DHF)/DSS patients are comparable with our findings.[11] In that study, the mean EF was reported to be 47% in 17 DHF patients and 39% in DSS patients. Depressed cardiac functions are an important component of viral VHF even in the absence of direct myocardial infection.[21] The depressed cardiac functions of our patients might have been due to involvement of the myocardium by the CCHF virus[12] and/or myocardial endothelial injury.[2,11,17,22] Further studies are needed to determine the pathogenesis of myocardial involvement in CCHF. We believe that depressed cardiac functions may cause shock and fatal outcomes in the severe form of CCHF.

In conclusion, CCHF presents with considerable cardiac involvement. We conclude that cardiac involvement during the course of the disease may affect fatality and the severity of CCHF, and thus, clinicians should be aware of this complication. Our study presents preliminary findings to enable and justify further studies, and describes for the first time in the literature the association between CCHF and cardiac abnormalities diagnosed by echocardiography, a frequently used noninvasive diagnostic tool for the evaluation of heart. We believe that further studies will show myocardial involvement in CCHF in the light of our initial findings.

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Conflict of interest: No conflict of interest to declare.

References

1. Whitehouse CA. Crimean-Congo hemorrhagic fever. *Antiviral Res* 2004;**64**:145–60.
2. Ergonul O. Crimean-Congo haemorrhagic fever. *Lancet Infect Dis* 2006;**6**:203–14.
3. Burt FJ, Swanepoel R, Shieh WJ, Smith JF, Leman PA, Greer PW, et al. Immunohistochemical and in situ localization of Crimean-Congo hemorrhagic fever (CCHF) virus in human tissues and implications for CCHF pathogenesis. *Arch Pathol Lab Med* 1997;**121**:839–46.
4. Bray M. Pathogenesis of viral hemorrhagic fever. *Curr Opin Immunol* 2005;**17**:399–403.

5. 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.
6. Ergonul O, Celikbas A, Baykam N, Eren S, Dokuzoguz B. Analysis of risk-factors among patients with Crimean-Congo haemorrhagic fever virus infection: severity criteria revisited. *Clin Microbiol Infect* 2006;**12**:551—4.
7. Vorou R, Pierroutsakos IN, Maltezou HC. Crimean-Congo haemorrhagic fever. *Curr Opin Infect Dis* 2007;**20**:495—500.
8. Joubert JR, King JB, Rossouw DJ, Cooper R. A nosocomial outbreak of Crimean- Congo haemorrhagic fever at Tygerberg Hospital. Part III. Clinical pathology and pathogenesis. *S Afr Med J* 1985;**68**:722—8.
9. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med* 2004;**32**:2416—21.
10. Savoia MC, Oxman MN. Myocarditis and pericarditis. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. 6th ed. Philadelphia: Churchill Livingstone; 2005. p. 1052—70.
11. Wali JP, Biswas A, Chandra S, Malhotra A, Aggarwal P, Handa R, et al. Cardiac involvement in dengue haemorrhagic fever. *Int J Cardiol* 1998;**64**:31—6.
12. Saggioro FP, Rossi MA, Duarte MI, Martin CC, Alves VA, Moreli ML, et al. Hantavirus infection induces a typical myocarditis that may be responsible for myocardial depression and shock in hantavirus pulmonary syndrome. *J Infect Dis* 2007;**195**:1541—9.
13. Oubiña JR, Milei J, Bolomo NJ, Molindo A, Carballal G. Experimental Argentine hemorrhagic fever: myocardial involvement in Cebus monkey. *J Med Primatol* 1986;**15**:391—7.
14. Kearney MT, Cotton JM, Richardson PJ, Shah AM. Viral myocarditis and dilated cardiomyopathy: mechanisms, manifestations, and management. *Postgrad Med J* 2001;**77**:4—10.
15. Obeyesekere I, Hermon Y. Myocarditis and cardiomyopathy after arbovirus infections (dengue and chikungunya fever). *Br Heart J* 1972;**34**:821—7.
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography; European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79—108.
17. Geisbert TW, Jahrling PB. Exotic emerging viral diseases: progress and challenges. *Nat Med* 2004;**10**(Suppl 12):S110—S121.
18. Ergonul O, Tuncbilek S, Baykam N, Celikbas A, Dokuzoguz B. Evaluation of serum levels of interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha in patients with Crimean-Congo hemorrhagic fever. *J Infect Dis* 2006;**193**:941—4.
19. Nagaratnam N, Siripala K, de Silva N. Arbovirus (dengue type) as a cause of acute myocarditis and pericarditis. *Br Heart J* 1973;**35**:204—6.
20. Pinamonti B, Alberti E, Cigalotto A, Dreas L, Salvi A, Silvestri F, et al. Echocardiographic findings in myocarditis. *Am J Cardiol* 1988;**62**:285—91.
21. Qian C, Jahrling PB, Peters CJ, Liu CT. Cardiovascular and pulmonary responses to Pichinde virus infection in strain 13 guinea pigs. *Lab Anim Sci* 1994;**44**:600—7.
22. Peters CJ, Zaki SR. Role of the endothelium in viral hemorrhagic fevers. *Crit Care Med* 2002;**30**(5 Suppl):S268—73.