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Does electrocardiography at admission predict outcome in Crimean-Congo hemorrhagic fever?

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ABSTRACT

Background & objectives: Crimean-Congo hemorrhagic fever is an acute viral hemorrhagic fever with considerable mortality. Despite increasing knowledge about hemorrhagic fever viruses, the pathogenesis of Crimean-Congo hemorrhagic fever and causes of death were not well described. We aimed to evaluate whether there were electrocardiographic parameters designating mortality among these patients.

Study design: This retrospective study was performed among confirmed Crimean-Congo hemorrhagic fever cases in Turkey. Electrocardiography was available in 49 patients within 24 h of hospitalization. All electrocardiograms were evaluated by two expert cardiologists according to Minnesota coding system.

Results: Among patients with available electrocardiograms, there were 31 patients who survived, and 18 patients who died of Crimean-Congo hemorrhagic fever. Both groups were similar in terms of age, sex, body temperature, heart rate, and blood parameters. T-wave changes and bundle branch block were more frequently encountered among those who died. Presence of T-wave negativity or bundle branch block in this cohort of patients with Crimean-Congo hemorrhagic fever predicted death with a sensitivity of 72.7%, specificity of 92.6%, positive predictive value of 88.9%, negative predictive value of 80.6%.

Conclusions: We think within the light of our findings that simple electrocardiography at admission may help risk stratification among Crimean-Congo hemorrhagic fever cases.

Key words Crimean-Congo hemorrhagic fever; electrocardiography; outcome

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic fever with 10–30% of case fatality rate. CCHF virus within the genus *Nairovirus* of the family *Bunyaviridae* is responsible for the clinical picture. CCHF was first described in the 1940s, and is now endemic in different regions of Africa, Asia, and eastern Europe. Human becomes 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 viraemic livestock. The most important clinical features are fever and in most severe cases, shock and hemorrhage. Despite, enormous amount of knowledge coming recently, causes of death are still not 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, still inadequate data are available on the cellular targets and distribution of CCHF virus in human tissues.

Refractory shock, severe coagulopathy and multifocal necrosis of the liver and other viscera are the modes of death[4]. Our group has recently demonstrated some echocardiographic findings associated with cardiac involvement among CCHF cases. However, electrocardiography (ECG) was not evaluated among these cases previously in literature. In this study, we aimed to show whether ECG, obtained in the hospital course of CCHF patients might help predict outcomes, mainly mortality, or not.

MATERIAL & METHODS

Study design

A total of 375, patients with suspicion of CCHF were admitted to the hospital betweeen 2007–08. Diagnosis was confirmed in 316 patients, 12-lead ECG recorded within 24 h of admission was available in 49 patients. All patients, who had confirmed diagnosis of CCHF and available ECG were enrolled retrospectively into our study. Electrocardiograms were manually evaluated by the use of a magnifying glass by two expert cardiologists (GB-MRE), blinded to patients' information and blinded to each other. In the case of disagreement, a third opinion was

obtained from another expert. Electrocardiographic findings were classified according to Minnesota code classification system. Abnormalities, noted in patients ECGs' were as follows: ST depression (Minnesota code 4.1.2: STJ depression ≥ 1 mm but < 2 mm and ST segment horizontal or downward sloping in any of leads V1, V2, V3, V4, V5), T-wave changes (Minnesota code 5.2: T amplitude negative or diphasic with negative phase at least 1 mm but not as deep as 5 mm in lead I or V6, or in lead aVL when R amplitude is ≥ 5 mm), early QRS transition zone (Minnesota code 9.4.1: QRS transition zone at V3 or to the right of V3 on the chest), complete right bundle branch block (RBBB) (Minnesota code 7.2.1), complete left bundle branch block (LBBB) (Minnesota code 7.1.1).

PR interval, QRS duration, QT interval and P-wave intervals were evaluated thoroughly. Normal QRS axis was accepted to be between –110 and +30 degrees. Abnormalities of the rhythm other than sinus were searched carefully. Left and right ventricular hypertrophy were searched accordingly[5,6]. Presence of any supraventricular or ventricular beat was evaluated.

QT intervals were taken from the onset of the QRS complex to the end of the T-wave, which was defined as the point T-wave returned to TP baseline[7]. R-R interval was used to compute heart rate in order to calculate corrected QT interval (QTc) with Bazett's formula.

The onset of the P-wave was defined as the junction between the isoelectric line at the beginning of the P-wave deflection and the offset of the P-wave was defined as the junction between the end of the P-wave and the isoelectric line. Maximum and minimum P-wave durations were measured, and then P-wave dispersion (defined as the difference between P-maximum and P-minimum) was calculated[8].

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 convalescent phase of the disease.

Statistical analysis

Demographics and ECG findings were recorded for each patient. Parametric data were expressed as mean ± SD or median (range) as required 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 $p \leq 0.05$ was accepted significant, using two-sided comparisons. SPSS (version 10.0) was used to perform statistical procedures.

RESULTS

Age, sex, platelet count, white blood cell count, body temperature and electrolyte levels were similar between groups (Table 1). There was no case with ST elevation and supraventricular or ventricular beat. None of the patients had electrolyte abnormality which could bring about ECG abnormality, during ECG recording. None of the patients had rhythm abnormality. All were in sinus rhythm. Patients in both groups were not different from each other concerning ST shift, QRS axis, heart rate, PR intervals, QRS duration, QT intervals and P intervals (Table 1). Of note, no patient had left or right ventricular hypertrophy signs. Furthermore, none was on digoxin therapy. There was complete agreement between two blinded experts who coded ECGs. Among patients who died of CCHF, early QRS transition zone, T-wave changes, LBBB or RBBB were more frequently encountered compared to those who survived CCHF (Table 1).

Presence of T-wave changes or bundle branch block (LBBB or RBBB) in this cohort of patients with CCHF predicted death with a sensitivity of 72.7%, specificity of 92.6%, positive predictive value of 88.9%, and negative predictive value of 80.6%. Presence of T-wave changes or bundle branch block (LBBB or RBBB) was associated with 33.333 fold (Odds ratio, 95% confidence interval 5.975–185.952) increased risk of death.

The ECG parameters with significance in the univariate analysis were enrolled into multivariable logistic regression analysis. It was found that T-wave changes (in the absence of LBBB or RBBB) (p=0.003, ExpB=17.668, 95% confidence interval 2.737–114.061), and presence of complete bundle branch block (mainly RBBB) (p=0.007, ExpB=39.882, 95% confidence interval 2.744–579.669) were found to be electrocardiographic independent predictors of death among patients with CCHF.

DISCUSSION

It has previously been demonstrated that hemorrhagic fever viruses could also cause cardiac involvement either in experimental or clinical studies. 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[9]. Dengue virus and yellow fever virus, the members of the flavivirus family can also cause cardiac involvement in humans[10-13]. A histopathological study by Burt *et al*[3] showed congestion and interstitial edema in the heart tissues of one fatal CCHF

Table 1. Comparison of demographics and electrocardiographic findings of Crimean-Congo hemorrhagic fever (CCHF) patients who survived versus who died

Variable	Patients who died (n=18)	Patients who survived (n=31)	*P*-value
Age (yr)	48.2 ± 21	48.6 ± 19.7	0.969
Sex (Male/female)	9/9	18/13	0.803
Heart rate (Beats per minute)	85 ± 18	81 ± 21	0.425
Body temperature (°C)	37.2 ± 1.1	37.4 ± 0.9	0.636
WBC count (per mm^3)	5.9 ± 6.2	3.4 ± 2.5	0.117
Platelet count (per mm^3)	36.5 ± 40.1	61.5 ± 45.1	0.05
Sodium (mEq/L)	135.6 ± 5.3	135.8 ± 2.8	0.841
Potassium (mEq/L)	4.2 ± 0.8	4.0 ± 0.5	0.258
PR interval (msec)	13.9 ± 2.5	15.2 ± 3.3	0.185
QRS duration (msec)	8.9 ± 1.9	8 ± 2.1	0.142
ST depression	3/18	4/31	0.697
Presence of normal QRS axis	15/18	25/31	0.815
QTcmax (msec)	417.2 ± 14.9	416.7 ± 12.6	0.903
QTc dispersion (msec)	28 ± 6.5	28 ± 7.2	1
Pmax (msec)	98 ± 10.6	99.3 ± 8.9	0.657
P-wave dispersion (msec)	30.8 ± 4.6	31.1 ± 5.6	0.823
Early QRS transition zone*	15/18	10/31	0.002
ST depression in V1–5	3/18	4/31	0.697
ST depression in V1–5 in the absence of LBBB or RBBB (compatible with coding)	1/18	2/31	1
T-wave changes	14/18	6/31	<0.001
T-wave changes in the absence of LBBB or RBBB (compatible with coding)*	9/18	5/31	0.02
Presence of LBBB or RBBB*	7/18	1/31	0.002
Persence of LBBB, RBBB or T-wave changes	16/18	6/31	<0.001
Presence of early QRS transition zone or RBBB or LBBB	15/18	10/31	0.001
Presence of ST depression or LBBB or RBBB	8/18	6/31	0.122
Presence of ST depression or, T-wave changes or LBBB or RBBB	16/18	9/31	<0.001

*Parameters enrolled into logistic regression, for Minnesota codes, please refer to manuscript; LBBB: Left bundle branch block; RBBB: Right bundle branch block; WBC: White blood cells.

case. The observation of cardiac congestion and edema in that fatal CCHF case may support cardiac involvement in CCHF infection. However, little is known about the effect of CCHF virus on the heart. We have recently shown that CCHF might involve cardiac structures as demonstrated by echocardiography[14]. However, so far, electrocardiography has never been considered in detail among these patients. Many viral diseases might induce ECG changes through involvement of cardiac tissues, which might respond via surface ECG abnormalities usually in mild forms.

It has been reported that certain ECG abnormalities associated with fatal outcome and/or clinical severity of some disease states. Bethell *et al*[15] studied electrocardiographic findings of patients with severe diphtheria and found the degree of ventricular ectopy at the time of presentation significantly associated with fatal outcome. In that study, more than two ventricular ectopic beats on a recording upon admission to the hospital predicted fatal outcome with 100% sensitivity and cent percent specificity. Salles *et al*[16] reported that electrocardiographic QT-interval dispersion (QTd) and echocardiographic LV end-systolic dimension were the most important mortality predictors in patients with Chagas' disease. That study demonstrated that both ECG ventricular repolarization parameters, QTcmax interval duration and QT interval dispersion, were important mortality risk predictors in patients with Chagas' disease. In this study, QT parameters were not different between those who died and those who survived of CCHF. None was found to have ectopic beats in the ECG recordings. However, presence of T-wave negativity and bundle branch block were associated with mortality.

In an experimental study, the electrocardiographic changes following rabbit coronavirus infection were examined. However, in that study, there were no significant

differences identified between ECG parameters measured in animals dying in the acute phase and those animals surviving into the subacute and chronic phases[17].

In the literature, we found several studies related to electrocardiographic findings of other viral hemorrhagic fever virus infections such as Lassa fever, dengue, and Hantavirus infections[18-24]. Cummins *et al*[18] found electrocardiographic abnormalities such as non-specific ST-segment and T-wave abnormalities, ST-segment elevation in patients with Lassa fever. In their study, none of the abnormalities correlated with clinical severity of infection. Electrocardiographic abnormalities as a result of dengue infection are common and have been reported to be in the range of 34–75%[19]. These are predominantly sinus bradycardia and conduction defects, all of which are transient. Hantavirus belonging to the Bunyaviridae family, the same family as that of the CCHF virus, causes haemorrhagic fever with renal syndrome (HFRS) is a systemic infectious disease.

Earlier reports describe different abnormal ECG findings during hantavirus infection. Basin *et al*[20] report on AV block in 2 patients with HFRS. Kim *et al*[21] described a case of torsade de pointes associated with hypopituitarism due to HFRS. In an another study, transient disappearance of hyperthyroidism with atrial fibrillation during the course of HFRS is described[22]. Kapetanoviae *et al*[23] found ECG alterations in 39 out of 43 patients with HFRS, mostly in the oliguric stage. The predominant finding was prolonged QT interval, followed by a tall and peaked T-wave. The authors concluded a tall and peaked T-wave and bradycardia in the oliguric stage to be pathognomonic of HFRS. Puljiz *et al*[24] also reported electrocardiographic changes in patients with HFRS. In their study, abnormal ECG was found in more than one-third of HFRS patients with the most common findings during the oliguric stage. Puljiz et al. determined ECG disorder such as sinus tachycardia or bradycardia, bundle branch conduction defects, non-specific ventricular repolarization disturbances, supraventricular and ventricular extrasystoles, prolonged QT interval, low voltage of the QRS complexes in standard limb leads, atrioventricular block first-degree, and atrial fibrillation in patients with HFRS.

There has been no study investigating electrocardiographic findings of patients with CCHF. In our study, mortal cases demonstrated variable degrees of ECG abnormalities. Particularly, T-wave changes and bundle branch blocks were noted to designate mortality. Of note, only one patient had left bundle branch block, and that patient survived, whereas 7 out of 7 patients with right bundle branch block died.

There are several reservations of the current study worthwhile mentioning. First of all, ECG is not part of a routine practice in follow up of cases with CCHF, and hence, ECG was present in a small group of patients with more severe disease. That was the reason for such high mortality, which is not the case in the overall population of cases with CCHF, in the cohort. Of note, this study was not performed to show mortality rate of CCHF, and hence, could give pieces of information for those patients who were referred to ECG. Therefore, findings should not be generalized to milder cases with CCHF. Furthermore, ECG findings are not specific for CCHF cases, and hence, could be observed in several other disease states. However, they are relatively easy to notice, and hence may help risk stratification particularly in the presence of baseline ECG, obtained at admission for comparison. It could have been better to incorporate cardiac biomarkers and other imaging modalities in order to show the timing and extent of any cardiac involvement in CCHF and to associate it with ECG findings. Besides, we did not have previous ECGs available though we did have the knowledge that no patient had previous history of heart disease. However, we think that ECG, as a potential marker of severity, might be part of follow-up of patients with CCHF, and physicians should be encouraged to obtain ECG samples both at admission and during follow up of these patients.

In conclusion, in this pioneering study, it seems that there are subtle ECG abnormalities among those who died up on CCHF infection compared to those who survived. Hence, at least among relatively severe patients, it might be important to obtain one ECG sample, which is easy and cheap, at admission to the hospital.

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