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Full Length Research Paper

Diagnostic criteria in Crimean Congo haemorrhagic fever disease and cost analysis

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In recent years, Crimean Congo haemorrhagic fever disease (CCHF) has created a serious health problem in our country. The disease takes place among haemorrhagic viral diseases. This study was made with CCHF diagnosed patients accepted in emergency services to determine the diagnostic criteria and cost effectivness for CCHF. CCHF patients who were accepted in our emergency service between 2004 and 2008 were analyzed retrospectively. Sensitivity, specificity, positive predictive and negative predictive value was calculated only for the patients who had 5 pathological laboratory parameters together (thromobcytopenia, high LDH, AST, ALT and CPK), and cost effectiveness analysis was made. During the five-year period, 687 patients had been evaluated. Significant pathologic results were established for alanine amino transferase (ALT), aspartate amino transferase (AST), creatine phosphokinase (CPK) enzymes, platelet counts and lactate dehydrogenase (LDH). Fatigue, fever, bleeding, gastro intestinal symptoms and diffuse pain were the symptoms seen according to their frequencies. The patients were frequently admitted in July. Mortality, costs per patient and emergency service's crowdedness can be reduced by rapid diagnosis which can easily be made with a brief history of the patient's occupation, physical examination and mentioned laboratory results sensitivity, specificity, positive predictive and negative predictive value.

Key words: Crimean-Congo haemorrhagic fever virus, emergency service, diagnostic criteria.

INTRODUCTION

Crimean Congo Haemorrhagic Fever was first seen in Crimea in 1944 and took the name Crimean haemorrhagic fever (CHF) but the viral agent could not be isolated. In 1956, a similar illness, with fever and haemorhagy, was identified in Congo among the soviet troops. In 1969, Chumakov et al. and Casals showed that the CHF disease virus and Congo haemorrhagic fever disease virus was antigenically indistinguishable. This realization and linkage of the two place names leads the scientists to the new name CHF-Congo virus was adopted to Crimean–Congo haemorrhagic fever virus in 1979 (Hoogstral, 1979; Ergonul, 2006). The virus which causes CCHF is a member of *Nairovirus* (family *Bunyaviridae*). CCHF is a severe disease in humans, with a high mortality rate. The CCHF virus infects a wide range of domestic and wild animals that serve as reservoirs for the virus. Ticks carry the virus from animal to animal or from animals to humans (Kara, 2006).

The most important source for acquisition of the virus by ticks is infected small vertebrate animals on which the ticks feed. Once infected, the tick remains infected through its lifespan. The mature tick transmits the infection to large vertebrates such as livestock (cattle, sheep and goats). Humans acquire the virus from direct contact with infected blood or tissues from livestock during this time, or they may become infected from a tick bite. After a short incubation period, a sudden onset of high fever, dizziness, abdominal pains, chills and severe headache symptoms are seen in CCHF disease. In addition, diarrhea, nausea, vomiting and cardiovascular changes can

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be seen also. Due to endothelial injury and liver failure, coagulatation factors cannot be activated and haemorrhagic manifestations, ranging from petechiae to large areas of ecchymosis develop in serious patients (Whitehouse, 2004). Symptomatic treatment is very important in CCHF. Ribavirin is also used as an antiviral agent but the benefits are controversial (Yen et al., 1985; Sheikh et al., 2005).

Moreover, the disease frequency has increased in recent years and while these viruses have the potential to be used as bioterrorism agents, it leads to a lot of attacks (Ergonul, 2006). CCHF frequency has been increased in Turkey in the last 6 years. Between 2002 – 2008, a total of 2500 case were reported in the Ministry of Health data and 5% of these cases died. CCHF is also an important issue since health care providers are under risk of transmission (Sheikh et al., 2005; Ergonul, 2008).

We aimed to display early diagnostic methods, which can be beneficial in decreasing the mortality- morbidity rates and costs. We want to create a diagnostic scale for CCHF to avoid confusions in healthcare facilities where the disease can be encountered more.

Table 1. Patients' distribution according to their admission months.

Months	Number of patients (%)
April	34(5%)
May	103(15%)
June	165(24%)
July	254(37%)
August	96 (14%)
September	27(4%)
Other	6 (1%)

Table 2. Symptoms distribution according to their frequencies.

Symptoms	Number of patients (%)
Fatigue	659 (96%)
Fever	625 (91%)
Pain	650 (95%)
Gastrointestinal system	515 (75%)
Bleeding	213 (31%)

MATERIALS AND METHODS

We checked 687 CCHF patients files retrospectively, whose diagno-sis were concretized by serological examination and infectious disease physicians, who were accepted in University Medicine Faculty Emergency Department, hospitalized and followed in infectious diseases service. Their epidemiological data, symptoms at the admission time and laboratory results were recorded in the forms. In addition, their professions, living regions and admission dates were recorded separately.

The routine laboratory tests ordered by emergency physicians for CCHF patients were as follows: Complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gama glutamyl transferrase (GGT), total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), creatinine kinase M-band (CK-MB), serum sodium (Na), potassium (K), calcium (Ca), D-dimer, fibrinogen, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Average cost prices of these laboratory tests for patients suspected having CCHF was calculated. Deaths during treatment were recorded. We calculated the sensitivity, specificity, positive predictive value and negative predictive value for the patients who had 5 pathological laboratory parameters together (thrombocytopenia, high LDH, AST, ALT and CPK) to decrease the costs and facilitate early diagnosis. Statistical analysis was made by SPSS 15.0. Standard deviation, distribution of frequencies sensitivity, specificity, positive predictive value and negative predictive values were calculated. The ethical approval number is 2008-12/2.

RESULTS

University Hospital is serving for about 2500.000 people population living in Sivas, Tokat, Giresun, Yozgat and Erzincan provinces. Patients come directly or are referred from these province hospitals.

Of the 687 patients included in this study, 367 (53.4%) were men, 320 (46.6%) were women. Youngest patient age was 16 and the oldest was 86 years. Mean age was 38 ± 17.29 years. Patients distribution according admission month time were shown in Table 1.

When the patients were evaluated according to their occupations, the rate for animal husbandry or agriculture was found to be 93% (639 patients). From all of the patients, 48% (330) had tick bite in their anamnesis.

The symptoms at the admission time were shown in Table 2 according to their frequencies. The laboratory tests ordered by emergency physician were analyzed and the mean ± standart deviaton, minimum and maximum values were shown in Table 3.

Average laboratory test costs ordered by emergency physician were calculated as 72 Turkish Lira (TL) (~45$)/ patient. Sensitivity, specificity, positive predictive and negative predictive value were calculated only for the patients who had 5 pathological laboratory parameters together and the results were shown in Table 4. Cost of these five parameters was only 8 TL (~5$).

DISCUSSION

In the last 6 years, CCHF was reported in Turkey with increased frequencies. Between 2002 and 2008, more than 2500 patients were admitted to hospitals. In our country, death rate from CCHF is around 5%. In recent periods, 8 health care providers were infected and this increased the importance of the disease (Ergonul, 2008; Bakir et al., 2005). In Turkey, CCHF was first reported from Tokat to the Ministry of Health, 2002. Yilmaz et al reported that the number of cases increased 5 times and

Table 3. Laboratory values.

	Mean	Minimum	Maximum	Normal
WBC	7.52±3.42	1.15	11.70	4-11 (10^3/µL)
NEUT %	53.40±4.47	5.10	87.30	41-73 (%)
HGB	13.35±1.58	7.30	17.20	4,2-5,4 (10^3/µL)
PLT	68.24±11.34	8.0	217	150-400 (10^3/µL)
INR	1.16±0,11	0.85	1.77	0,89-1,1
BUN	15.21±5.16	5.0	57.0	8-20 mg/dL
CREATININE	0.91±2.20	0.40	2.10	0,4-1 mg/dL
AST	253±109,58	17	1447	15-41 IU/L
ALT	125±54.17	10	491	14-54 IU/L
LDH	614±223.56	136	2039	125-240 IU/L
CPK	463±228.12	18	4184	38-234 IU/L
CKMB	17.22±7,16	1.40	44	2-18 U/L
ESR	14.48±22.82	0.0	44	Age/2+10/2*mm/h
CRP	21.56±41.78	1.0	204	0-6 mg/dL
F BR NOGEN	276±52,60	132	385	200-400 mg/dL
D.DiMER	1028±1060,76	208	3699	<150 ng/ml
GGT	84±41.42	6	524	0-36 mg/dL
T.B L RUB NE	0.84±0.43	0.40	3.80	0.1-1 mg/dL
C.B L RUB NE	0.22±0.19	0.10	0.90	0.1-0.3 mg/dL

WBC: White blood cell, PLT: platelet, INR: International normalized ratio, BUN: blood urea nitrogen, AST: aspartate amino transferase, ALT: alanine amino transferase, LDH: lactate dehydrogenase, CK: kreatinin kinase, CKMB: creatinine kinase M band, ESR: eryhtrocyte sedimentation rate, CRP: C reactive protein, GGT: gama glutamyl transferase, T.BILIRUBINE: total bilirubin, C.BILIRUBINE: conjugated bilirubin. * For females.

Table 4. Diagnostic test results for 5 pathological laboratory parameters.

Sensitivity	85.23%	82.33 to 87.82%
Specificity	82.29%	79.05 to 85.21%
Positive Predictive Value	83.99%	81.03 to 86.65%
Negative Predictive Value	83.63%	80.46 to 86.48%

the mortality number increase 6 times from 2002 until 2008. The mortality/morbidite rates were as follows according to their years: 6/150 cases in 2002 and 2003, 13/249 cases in 2004, 13/266 cases in 2005, 27/438 cases in 2006, 33/717 cases in 2007 (Yilmaz et al., 2009). Increasing incidence and mortality numbers threatens the people in Turkey more and more.

Since CCHF is transmitted via ticks and while they are present everywhere where there are animals, that is why prevention of the disease is difficult. Wild animals and livestocks carry ticks. Therefore early diagnosis in human is more important than isolation of ticks for transmission of the disease. We aimed to facilitate the diagnosis and managements with this study while large number of patients with CCHF disease susceptibility admitted to emergency departments, especially in summer months.

The gender rate (male and female) in CCHF disease was (64 and 36%, respectively) in Sheikh et al., study and (50 and 50%) in Bakir et al., study made in central Anatolia region (Sheikh et al., 2005; Bakir et al., 2005). Yilmaz et al found male/female ratio as 1.07 (Yilmaz et al., 2008). In our study, we found 53.4% males and 46.6% females. Our results are consistent with the upper studies in Turkey, but not compatible with Sheikh et al's study done in Pakistan. This can be due to differences in living conditions and male/female working rates.

CCHF disease was seen mostly in June, July, May, April and March in order of frequencies (Yilmaz et al., 2008). In another study, highest percentages of the disease were seen in June and July (Kara, 2006). Our data was compatible with these studies.

Bakir et al found that 90% of patients were engaged with agriculture and 60% of patients had a tick bite history (Bakir et al., 2005). Yilmaz et al reported also that most patients were engaged with livestock and agriculture (Yilmaz et al., 2008). In our study, data was compatible with these studies. Our results resembled the two studies that peoples are in high risk group if they are living in rural areas engaged with agriculture and livestock. According to Sheikhs et al study, the symptoms at the time of admission for CCHF patients were as follows: 83% fever, 45% GIS symptoms, 83% pain in various parts of body and 100% bleeding (Sheikh et al., 2005). In another study 86% fatigue, 73% fever, 80% pain, 75%

GIS symptoms and 48% bleeding were established (Bakir et al., 2005). In our study, the admission symptoms were 96% fatigue, 95% pain, 91% fever, 75% GIS symptoms and 31% bleeding. Although admission symptoms are largely alike, bleeding and GIS symptoms rates difference compared with Sheiks study can be explained by calculating the admission time, concomitant disease or drug use which affects the coagulation and bleeding time. Because of the high ratios of these symptoms among CCHF patients, these should be kept in mind to facilitate the diagnosis.

Among some studies, we found that platelet, ALT, AST, LDH and CPK laboratory values were increased significiantly. Karti et al., detected the laboratory values as follows: Platelet, 15 x 10^3/µL; ALT/ AST, 248/693 IU/L; LDH, 1601 IU/L; CPK, 568 IU/L (Karti et al., 2004). Bakir et al found mean laboratory values as follows: Platelet, 53 x 10^3/µL; ALT/ AST, 148/146 IU/L; LDH, 1164 IU/L; CPK, 401 IU/L (Bakir et al., 2005). Sheikh et al mean laboratory results were reported as; Platelet, 27.1 x 10^3/µL; ALT/ AST, 46/409 IU/L (Sheikh et al., 2005). In case report of Bozkurt et al., laboratory values were reported as follows: Platelet, 14 x 10^3/µL; ALT/ AST, 766/1895 IU/L; LDH, 2611 IU/L (Bozkurt et al., 2005). In another study, platelet counts was 5 x 10^3/µL; ALT/ AST, 360/632 IU/L and CPK, 210 IU/L (Jauréguiberry et al., 2005). Yilmaz et al reported that platelet levels lower than 150 x 10^3/µL and the increase of ALT, AST, LDH, CPK enzyme levels in serum levels had an important value in the diagnosis of CCHF (Yilmaz et al., 2008). In our study, mean laboratory values were as follows: Platelet count, 68.24 x 10^3/µL; ALT 125, IU/L; AST, 253 IU/L; LDH, 614 IU/L and CPK, 463 IU/L. It is obvious that in all these studies, five laboratory tests (platelet, AST, ALT, LDH and CPK) were pathologic. That is why we calculated the sensitivity, specifity, positive predictive and negative predictive value for the patients with pathologic values of the 5 parameters to estimate CCHF diseases diagnosis (Table 4). According to our study, the diagnosis of CCHF can be made easily and with 85.23% sensitivity and 82.29% specificity by taking the patients history about their occupation, presence of fatigue, fever, pain, bleeding symptoms and managing the platelet, ALT, AST, LDH and CPK values together.

In patients prediagnosed with CCHF or fever of unknown origin, CBC, PT, aPTT, BUN, kreatinin, ALT, AST, LDH, CPK, CKMB, GGT, bilirubins, Na, K, Ca, D-dimer, fibrinogen, ESR, CRP laboratory tests are ordered. The cost of these tests is 72 TL (~45$). That brings a very heavy burden on national economy. These 5 tests (Platelet, LDH, AST, ALT, CPK) costs only 8 TL (~5$).

Also acting in this way, eliminating unnecessary laboratory orders, will probably decrease loss of time. This can ease the patient flow especially in emergency departments and early diagnosis and treatment can decrease the mortality.

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