

CLINICAL CHARACTERISTICS OF CRIMEAN CONGO HEMAORRHAGIC FEVER: EXPERIENCE AT A TERTIARY CARE HOSPITAL IN KHYBER PAKHTUNKHWA

Ziauddin, Inayat Ullah, Muhammad Kashif, Naveed Iqbal, Khalid Mahmood

Department of Medicine, Lady Reading Hospital, MTI, Peshawar, Pakistan

ABSTRACT

Objective: To describe the clinical manifestations and laboratory features of Crimean Congo Hemorrhagic Fever (CCHF).

Material and Methods: The study was conducted at Lady reading Hospital, MTI, Peshawar from July 2017 to July 2018. 112 suspected cases of CCHF were included. Their demographics, clinical features and laboratory findings were recorded on pre-designed proforma. Blood samples were sent to NIH, Islamabad for testing RT-PCR and CCHFV antigens and anti-CCHFV antibodies. Data was analysed by SPSS version 21.

Results: 15 cases were found to be positive for CCHFV by RT-PCR and CCHFV antigens. Almost fifty percent of the studied patients were butchers by profession. Fever, headache and petechial hemorrhages/bruises were the most common presenting complaints. Thrombocytopenia (platelet count less than 150,000) was the most common laboratory finding followed by deranged liver function tests and abnormal coagulation profile. Overall mortality was 33.3%.

Conclusion: CCHF carries high mortality with limited treatment options. Health authorities should focus on the primordial and primary prevention of the disease.

Key Words: Crimean Congo Hemorrhagic Fever, Thrombocytopenia, RT-PCR

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INTRODUCTION

Crimean Congo Hemorrhagic Fever (CCHF) is an acute viral infection caused by Crimean Congo Hemorrhagic Fever Virus (CCHFV).¹ It is an RNA containing virus that belongs to the Genus Nairo and family Bunyviridae. It is an arboviral zoonotic infection that is transmitted to human beings by tick bite or contact with blood, secretions or tissues infected with CCHFV.²

The disease was first reported in 1944 when more than 200 cases in USSR troops in Crimea. Later on similar cases were reported from Congo in 1956. In 1969, Casals found antigenic similarities between viral strains isolated in Crimea and Congo. Hence named as CCHF. Since then the disease expanded to different parts of the world including Africa, Asia, Europe, Mediterranean

Region, China, Middle East and Indian Subcontinent.^{3,4}

In Pakistan, the first strain was isolated in 1960 from tick species. But the first case was reported in 1976 at General Hospital Rawalpindi.^{5,6} 23 cases of CCHF with mortality rate of 39% were reported between 1976 and 2000.^{7,8} Since 2000, the disease is rising exponentially. Around 50 to 60 cases are reported every year particularly in the month of June and October. There was an outbreak of the disease in our country in 2013 when 61 cases reported with 17 deaths and mortality of 27.8%. Majority of the cases were reported from Baluchistan province followed by other provinces.⁹ In our province, KP, the first case was reported in 2005 in District Abbottabad in September 2010, an outbreak of CCHF got concern when the blood samples of a young doctor in Bisham, while managing a patient with hemorrhagic fever, developed same symptoms and ultimately died of it, revealed CCHF. At the moment the disease is endemic in our country with sporadic outbreaks.⁵

The clinical spectrum of the disease is very wide ranging from none or mild symptoms to fatal hemorrhages. Generally the clinical course of the disease is divided in four phases that includes: Incubation phase,

Dr. Inayat Ullah (Corresponding Author)

Assistant Professor

Department of Medicine, Lady Reading Hospital, MTI, Peshawar, Pakistan

E-mail: drabadat78@yahoo.com

Contact: 0092 300-5862093

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Pre-hemorrhagic, hemorrhagic and convalescent phase. The incubation period lasts for three to seven days after acquiring the virus. Pre-hemorrhagic phase proceeds incubation periods that lasts for 4 to 5 days characterized by fever, pain abdomen, myalgia, low BP and facial flushing.¹⁰ Hemorrhagic phase comes next that is characterized by petechiae, ecchymosis, bleeding from gums, hematemesis, nasal and rectal bleed.^{2,11,12} Convalescent phase is the phase of recovery in patients who survive the disease starting 10 to 20 after the onset of illness.¹⁰

CCHF is highly fatal disease. Overall fatality rate of CCHF is 10-40 %. 13 Reported cases fatality rate of 30% in Iran and 27.8% in Pakistan.¹⁴⁻¹⁷ Multiple factors are responsible for the worst outcomes of this disease like shock, multi-organ failure, thrombocytopenia and hemorrhages.⁵

Although CCHF is a matter of high public health concern due to its exponentially rising distribution, high mortality rate and lack of specific treatment and vaccines leaving behind prevention as the best possible remedy at the moment, the work up done so far for better understanding of this disease is very limited in our country particularly in our province creating a gap in the awareness among the general population. Therefore in this study we will describe the clinical and lab manifestations and the factors responsible for worst outcomes of CCHF presented to tertiary care hospital in KPK aiming at the early identification, prompt therapy and isolation of the patients infected with CCHFV and better understanding of CCHF and make recommendations to public health authorities to avoid any future outbreaks of the disease.

MATERIAL AND METHODS

This retrospective study was conducted at Medical C unit of Lady Reading Hospital Peshawar, Pakistan and the record of 112 patients admitted between July 2017 and July 2018 with fever and thrombocytopenia (platelet count < 150,000 × 10⁹/L) were reviewed. Lady Reading Hospital is an 1800-bed public sector, tertiary care teaching hospital serving almost 1.97 million population of Peshawar City.

Viral Hemorrhagic Fever (VHF) were suspected on the basis of clinical features such as high grade fever, myalgia, severe headache, nausea and vomiting. Epidemiological risk factor like history of tick bite, contact with suspected cases of VHF, or contact with animal blood or carcasses, travel to or residence in an area of endemicity of CCHF (Karak, LakiMarwat districts) and suggestive laboratory investigations which include anemia, leucopenia (WBC count < 3000 × 10⁹/L) and thrombocytopenia. Viral cultures were not available

for the diagnosis of VHF. Blood samples for these suspected cases of VHF were collected within the first 5 days of admission and stored at -800C. These samples were later on sent to NIH (National Institute of Health, Islamabad) where they were screened for CCHF antigens, anti CCHF IgG and IgM antibodies and reverse transcriptase PCR (RT-PCR). Other laboratory parameters like FBC, PT, aPTT, INR, LFTs, Blood Urea, serum Creatinine, FDPs were also performed in these patients.

Demographic characteristics including age, gender, occupation and clinical and laboratory features were also recorded. Data entry and analysis was done through SPSS version 21. Statistical significance was set at *p* value < 0.05. For numerical values like age, mean + SD as calculated while for categorical features like gender and clinical features, frequencies and percentages were calculated.

RESULTS

A total of 15 confirmed cases of CCHF who met the clinical criteria and also serological tests results that were positive for IgM or IgG CCHF virus specific antibodies by ELISA or genomic segment of the CCHF virus by RT-PCR were studied. Of these, 13 (86.7%) were male and 2 (13.3%) were female. Male to female ratio was 6.5: 1. All female patients were house-wives. Age of the patients ranged from 17 to 70 years with mean age of 38 ± 13 years. Majority of cases were below 50 years. We recorded patients in two major groups. Group 1 consisted of those whose occupation placed them at high risk like butchers (46.7%), livestock businessmen (20.0%), lab technicians, physicians, nurses and groups 2 consisted of those patients whose occupation was considered safe e.g. house hold workers (13.3%) and students (20.0%). History of tick bite was obtained in one patient (6.66%) and contact with animal blood or carcasses 14 cases (93.33%).

Our patients were from different districts of KPK. All the patients were treated in local hospitals where

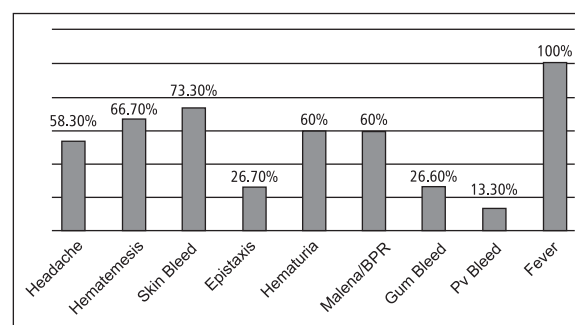


Figure 1: Presenting complaints of patients with CCHF

Table 1: Laboratory Features of patients with CCHF at presentation

Labs (at presentation)	N(# of Patients)	Minimum	Maximum	Mean	Std. Deviation
HB(gm%)	15	7.8	16.0	12.880	2.0407
TLC	15	2200	18900	8712.67	4961.147
Platelet Count	15	6000	95000	40933.33	30527.427
PT in seconds	15	14	60	22.40	14.382
INR	15	1.0	5.0	1.717	1.3590
aPTT in seconds	15	30	60	38.00	10.289
ALT	15	72	408	174.60	88.904
Serum Bilirubin	15	.20	4.10	1.1680	.98118
Serum Creatinine	15	.61	2.31	1.0020	.45097
Blood Urea	15	24	98	49.13	20.911

they had presented with clinical manifestations and then referred to Lady reading Hospital, Peshawar. Most of the patients were reported to be from Peshawar (33.3%). 4 patients (26.7%) belonged to district Karak while one patient each from district Mardan and Swabi. Four of our patients were inhabitants of FATA (26.7%, 02 from Bajaur Agency and 02 from Mohmand Agency) as shown in the table.

The mean duration of symptoms was 7.1 days (range 4-11 days) at the time of admission. Fever and skin bleed were the most common presenting complaints. Fever was initially high grade (up to 102°F). However the patients who recovered became afebrile during the hospital stay. Other clinical manifestations either on presentation or during the hospital stay were gastrointestinal bleeding and bleeding from other sites of the body as shown in the figure 1. Petechiae and/or bruises were seen in eleven patients (73.3%). Four patients developed hematuria (60.0%) and vaginal bleed (13.3%) manifested between four and ten days after onset of symptoms. Our mortality was 33.3%.

As far as laboratory features are concerned total leukocyte count varied between 2200 and 18900. Leucopenia (TLC<4000) was seen in ten patients from day 4 to day 12 of onset. Five patients who had marked leucopenia (TLC<3000) died while five patients who survived had counts more than 3700. On average total white cell count drop to mean of 2700 in those who died while in those who survived it was 3800. Low Hb was noted during early phase of illness. The mean value of Hb was 12.8gm/dl(range 7.8-16.0). All patients were thrombocytopenic (platelet less than 150×10⁹). Platelet counts varied from 6-95×10⁹. Disseminated intravascular coagulation was seen in all the five patients with prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). The mean value of PT in survivors was 12.6seconds (control 13seconds, range

10.5-14.7seconds) with mean INR of 1.00, while the mean PT in those who expired was 22.4seconds (range 14.0-60 seconds) with mean INR of 1.71.

Liver function tests were deranged in those who died. Total bilirubin (range 0.61-4.10) and liver enzymes were elevated. Mean ALT was 174.6IU/L (range 72-408). Serum creatinine remain normal (<1.1mg/dl) in those who survived but was elevated in all five patients who expired (range 1.4-2.31mg/dl).

DISCUSSION

CCHF is endemic and enzootic in different areas of Pakistan⁸. Over the last two decades, Pakistan has faced significant public health care challenges including the outbreak of polio and dengue fever. In 2000, a lethal epidemic of CCHF hit Pakistan^{4,18}. Pakistani population is at high risk of acquiring CCHF due to a variety of risk factors. These include underdeveloped health care system^{6,19}, lack of general public awareness regarding the spread and control of the vector²⁰. In our study 46.7% of the patients were butcher by profession. Both urban and rural butchers are high risk group for CCHF. In our country there are countless meat shops in every small and big cities. These shops are open-aired, unhygienic stalls where the butcher chop the meat bare-handed, while the un-skinned bodies of animals are hanged in front of the customers. Chopping the meat of an infected animal without gloves and without proper hygienic measures, butcher can easily be infected through minor cuts.

20.0% of our study belonged to livestock business. Pakistan has a vast livestock population and because of this a large of humans are in contact with animals on daily basis²¹. Also these people are involved in different work practices such as veterinary care, birthing procedures etc that can be a source of animals to human transmission of CCHF. A study from Afghan-

istan in 2009 reported that people who are involved in animal slaughtering and butchering and removing ticks bare-handed have greater chance of getting CCHF virus²².

Among the 12 studied patients, six were hospitalized from 1st week of August to 3rd week September 2017. This period coincided with the transit of sacrificed animals from Baluchistan province and Afghanistan to KPK for the Islamic Festival of Eid-ul-Azha. Afghanistan has reported to have a high prevalence of CCHF²². The dates of Eid-ul-Azha concurred in the summer in Pakistan in this decade. Majority of people purchased cattle, sheep and goats and keep them at the houses for a few days before the Eid festival. This constitutes a chance of transmission of CCHF in humans via the bite of an infected tick. In our setup, sacrifice always take place on streets and roadside footpaths and always involve close contact between animals and humans. After slaughtering the animals, the residual were thrown in open places, thereby increasing the chance of CCHF²³.

The time interval between the disease onset and admission (mean 7.1 days) in the patients of the current study was longer. The corresponding average interval in patients from Turkey 5.5 days^{11,12} Iran 4 days¹⁵ and UAE 3.5 days²⁴. It may be because of disparity in the local health system. Clinical manifestations of CCHF demonstrated in our patients are almost similar to those described in other studies.²⁵

CONCLUSION

As primary care physician, CCHF should be considered in every patient having history of contact with infected animals, travel to endemic areas, clinical features like pyrexia of unknown origin with bleeding from any part of the body and laboratory findings including platelet count less than 150,000 cells/mm³ and deranged liver function tests and coagulation profile.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

- Ziauddin:** Study conception and design, data collection and manuscript writing, final approval.
Ullah I: Data interpretation, data collection.
Kashif M: Data analysis and interpretation, bibliography and manuscript writing.
Iqbal N: Bibliography.
Mahmood K: Critical review of the manuscript.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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