

Case Report

An epidemiological study of patients admitted with viral hemorrhagic fever (VHF): A single center experience

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Objective: To evaluate the epidemiologic characteristics of dengue and Crimean-Congo hemorrhagic fever (CCHF) and to assess the impact of admission platelets on total hospital stay and final outcome.

Methodology: This cross-sectional observational study included 300 patients with dengue and 11 patients with CCHF. Patient's outcome was measured in terms of death or recovery and relationship between admission platelets and total hospital stay was assessed. Independent sample t-test and Chi square tests were used for statistical analysis.

Results: In dengue patients, the mean age was 30.60 ± 9.70 years, against a mean age of 36.82 ± 11.74 for CCHF. The mean hospital stay was shorter for dengue (5.7 ± 0.83 days), than for CCHF (7.91 ± 7.44 days). The mortality rate for dengue was much lower (2%), than that of CCHF (36%). In dengue patients, death was more

prevalent in females [$n=2$ (8.7%), and $Z=2.4$], than in males [$n=4$ (1.4%), and $Z=2.4$], at a statistically significant level, Chi square (1) = 5.69, $P=0.01$, $\Phi=0.14$. However, more men died of CCHF than females ($p<0.05$). Shock and coagulopathy were more common in CCHF than dengue. Moreover, increasing age increased mortality in both CCHF and dengue fever ($p<0.05$). Contrary to patient's age, platelet count on admission did not influence the final outcome ($p>0.05$).

Conclusion: Mortality from CCHF was much higher than that from dengue fever. Death from CCHF was commoner in males. However, dengue related deaths were commoner in females. Patient's age, but not the initial platelet count worsens the final prognosis. (Rawal Med J 201;42:479-483)

Key words: Dengue, outcome, mortality, Crimean-congo fever, bleeding.

INTRODUCTION

Dengue is a disease caused by one of the four serotypes of dengue virus (DEN 1-4), transmitted by *Aedes Aegypti*. Infection by one serotype causes acute illness and provides long-term immunity. However, sequential infection by a different serotype in future, causes more serious illness.¹⁻³ The clinical spectrum of dengue ranges from less severe 'dengue fever' (DF), to more serious febrile illness called as, 'dengue hemorrhagic fever' (DHF), or even in most severe cases to shock, termed as 'dengue shock syndrome' (DSS).³⁻⁵

The first ever deadliest outbreak of Crimean-Congo hemorrhagic fever (CCHF) virus was reported in the 1940s in the Crimean peninsula.⁶ CCHF having a case fatality rate of around 50-60% in humans, is caused by virus belonging to the family *Bunyavirida*. On the basis of genetic variability, the

Congo virus has been divided into seven serotypes including; Africa-1, Africa-2, Africa-3, Europe-1, Europe-2, Asia-1 and Asia-2. Because of very high fatality rates and alarming pathogenic nature of CCHF, there is a possible risk of this virus being used as an agent of bioterrorism or as biological warfare. Therefore, the culturing of this virus is only permitted in bio-safety level four (BSL-4) and in maximum secured laboratories. It is transmitted to humans by tick bites directly or through contact with the blood or body fluids of diseased animals or human as in the hospital. CCHF is endemic in different regions of the world including Africa, Southeast Europe, Middle East and Asia.⁷

In 1994, an outbreak of dengue was reported in Pakistan. Since then, many outbreaks have threatened the Pakistani people. An increased prevalence of dengue has been reported in Pakistani

people living in slums.⁸ As the virus is widely distributed in the world, Pakistan has experienced the epidemics of this disease every now and then, covering almost all four provinces of Pakistan.⁹ Preventive measures are crucial in eradicating the virus from the country, as subsequent to poliovirus, CCHF may become a serious threat Pakistanis.^{9,10} It must be noted that, in September 2010, an epidemic was reported in the KPK province of Pakistan. Although, the record keeping was not standard, some reports indicated cases in excess of hundred, with a case-fatality rate above 10%.⁷ The aim of this study was to evaluate the epidemiologic characteristics of dengue and CCHF in our area and to assess the impact of admission platelets on total hospital stay and final outcome.

METHODOLOGY

This cross-sectional, observational study was conducted in the department of medicine of Khyber Teaching Hospital (KTH), Peshawar, Pakistan from July to December 2015. For the purpose of prevention of infection, the suspected patients were admitted to special isolation suite in KTH. Universal precautions were adopted while handling such patients. The study included 300 patients diagnosed with dengue and 11 patients diagnosed with CCHF. Informed written consent was obtained from every participant and study was approved by the hospital's Ethics committee.

The inclusion criteria included both genders, any age range, NS-1 antigen positivity for dengue, confirmed dengue cases irrespective of prior history of dengue, and positive polymerase chain reaction (PCR) for CCHF. Those not fulfilling the above mentioned criteria, those having alternative or co-existent diagnoses like malaria, infectious mononucleosis, HIV, septicemia, disseminated intravascular coagulation (DIC), immune thrombocytopenic purpura (ITP), hematological or solid organ malignancy, liver cirrhosis, hypersplenism, immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), medications affecting blood platelet count like chemotherapeutic agents and so forth, were excluded.

A questionnaire included questions regarding demography, co-morbidities, signs and symptoms, complete blood picture, dengue serology, NS-1 antigen positivity and PCR results for CCHF. Dengue tests were performed by using ELISAs (In Bios International, USA). CCHF was confirmed by performing PCR (VetPCR™ CCHF Detection Kit, VET-CA004-48R, Bioin Gentech, Chile). All the data was analyzed by using SPSS version 16. Chi-square test was run to stratify the different test variables like platelet count and age, with respect to the outcome, death or recovery. $p < 0.05$ was considered as significant.

RESULTS

Patients with dengue fever: Out of 300 patients, 277 (92.3%) were males and 23 (7.7%) were females. The mean age was 30.60 ± 9.70 years. In terms of the final outcome, 294 (98%) recovered. However, 6 (2%) patients died. The mean alanine aminotransferase (ALT) on admission was 48.73 ± 9.71 IU/L.

The mean hospital stay in days for every participant was 5.7 ± 0.83 (range 4-8). Platelet transfusion was needed in 16 (5.3%) patients. The mean number of pools of platelets transfused was 0.10 ± 0.48 (maximum 4). Nine patients (3%) were transfused only one pack of platelets. However, the number of patients who received more than one pack of platelets was 7 (2.3%) (Table 1).

Table 1. Comparison of platelet count on admission and on discharge/death.

Variable	Mean	SD	Minimum	Maximum
Patients with dengue fever				
Platelet count on admission (per mm ³)	57,000	5477.07	33,000	67,000
Platelet count on discharge or death (per mm ³)	133,000	16377.18	31,000	151,000
Patients with CCHF				
Platelets on admission (per mm ³)	64300/mm ³	21256	24,000	100,101
Platelet count on discharge or death (per mm ³)	35,759	10,090	15,000	65,000

Death related outcome was more prevalent in females (%=8.7, and $Z=2.4$) than in males (%=1.4, and $Z=2.4$, at a statistically significant level, Chi

square (1)=5.69, $p=0.01$, $\Phi=0.14$. Similarly, more patients [$N=6$ (5.5%) and $Z=0.7$], belonging to Peshawar area, died than the rest of the province. However, the difference was not statistically significant, Chi square (1)=0.51, $p=0.48$. Patients presenting with fever and aches alone, died more than those presenting with rash or other symptoms like cough, anorexia and so forth, [$N=5$ (2.1%), Z score=0.2]. However, the death related difference between different type of clinical presentation was not significant statistically, Chi square (2)=0.09, $P=0.95$. Admission platelets counts did not influence the final outcome or hospital stay, $p>0.05$. However, more elderly patients died of dengue than the youngsters ($p<0.005$).

Patients with CCHF: There were more males [$(N=10)$, (90.9%)], than females [$(N=01)$, (9.1%)]. The mean age was 36.82 ± 11.74 (range 25-60). By profession, butchers, farmers and others, constituted 45.5%, 18.2% and 36.4%, respectively. 45.5% patients each belonged to Peshawar or other parts of KPK, while 9.1% of the cases were from Afghanistan. Of all the cases of CCHF, 63.6% recovered and were discharged and 36.4% died. The mean hospital stay in days was 7.91 ± 7.44 (range 1-27). Mean platelet count on admission was $64300/\text{mm}^3 \pm 21256$. Main clinical manifestations of the patients are summarized in Table 2.

Table 2. Comparison of the chief clinical characteristics of the patients of the two groups.

Clinical Feature	Patients with Dengue	Patients with CCHF
Fever	85.7%	50%
Myalgias	71.4%	75%
Headache and eye pain	71.4%	75%
Conjunctival Ingestion	57.14%	75%
Hepatomegaly	42.85%	50%
Coagulopathy & Shock	42.85%	80%
Purpura	28.5%	75%
Mean hospital stay	< 1 week	>1 week
Mortality	2%	36.7%

Age of the patients who died was higher ($M=45.75$, $SD=14.29$), than those who survived, ($M=31.71$, $SD=6.62$), at a statistically significant level, $t(9)=2.27$, $p=0.04$. Nevertheless, the total hospital

stay was higher in patients who recovered, (11.43 ± 7.23), than those who died, (1.75 ± 0.5). Again the difference in hospital stay between the two groups was statistically significant, $t(9)=2.61$, $p=0.02$. Although, the platelet count on admission was higher in the recovery group, (70700 ± 21876), than the expired group, (53000 ± 16812), but the difference between the two study groups was not significant statistically, $t(9)=1.39$, $p>0.05$.

DISCUSSION

Our study demonstrated that both CCHF and dengue fever are commoner in males. This is in accordance with previous studies.^{7,10,11} Maximal cases reported in male population are probably because; they are more exposed to bites by aedes aegypti, as they work out side. Moreover, females are protected by their long and heavy clothes, which keep them covered most of the times.^{7,10} Aedes aegypti likes living in hot and humid habitats. Similarly, tick bites by CCHF's vector are common during pilgrims and Eid-ul-Adha. The coincidence of these two explains the high prevalence in the months of monsoon rains and Eid-ul-Adha. In our study, a gradual increase in cases was seen from July to September. A local study had similar observations; the incidence of these diseases peaking in the months of September-November.¹¹ In the present study, most of the patients were in their 3rd-4th decade of life. This is in accordance with previous observations.¹⁶ Moreover, most of the death were seen in those in the fifth decade of life as seen in other South-Asian studies.^{12,13}

The clinical manifestations of viral hemorrhagic fevers are variable. However, the commonest clinical characteristics are fever, aches and pains, retro-orbital heaviness, rash and so forth.^{18,19} Majority of patients in our study had presented with fever and aches. It must be noted that, all these symptoms might have an abrupt onset. Moreover, viral hemorrhagic fevers lead to bleeding tendency from various parts of the body including mucosal or even deadliest intra-cerebral hemorrhages.^{14,15} Such bleeding may compromise the circulation and result in shock called as DSS.^{16,17} However, despite aggressive measures, the outcome is usually poorer in such patients. Such patients needed ionotropic

support and multiple platelet transfusions.¹⁴⁻¹⁷ Our study showed that shock was more common in patients with CCHF than those with dengue. The development of early and aggressive shock and coagulopathy in patients with CCHF might explain the higher mortality associated with it.

In Pakistan, the CCHF virus was first isolated for the first time in 1960 from Hayaloma species of the ticks. Between 1976 and 2000, only 23 cases of CCHF were reported in Pakistan with a case fatality rate of 39%.¹⁸ It is interesting to note that, only in the year 2016, 11 cases were confirmed at KTH Peshawar alone with a case fatality rate comparable to the previous studies.^{18,19} This might explain either an increase in the burden of CCHF in our country or unreported previous cases or both. Moreover, the better and widespread availability of diagnostic tests for CCHF may be another plausible explanation. The CCHF virus is transmitted to human either by tick bites or through intimacy with blood or tissues of the infected animal during or immediately after slaughter.¹²⁻¹⁴ It must be noted that, majority of patients in our study sample (81%), had evidence of known contact with livestock or infected person.

The diagnosis of viral hemorrhagic fever can be confirmed in a number of ways. This depends upon the pathogens. However, the currently available laboratory tests include serology, antigen detection, PCR for CCHFV, and virus isolation by culture. We confirmed all the cases by doing PCR for CCHFV and NS-1 positivity for dengue fever.^{9,12} For both the illnesses, treatment is through general supportive measures. There is still some controversy regarding the effectiveness of ribavirin in the treatment of CCHF. There is no effective vaccine available for protection against CCHF or dengue. Nevertheless, preventive measures like wearing protecting clothing, use of insecticides to kill the vector and adapting universal personal protective precautions and so forth, are the only source of hope against these deadly diseases.^{8,10,17}

One of the limitations of our study was that the catchment area was small. Secondly, patients admitted to general medical wards only were included and those in pediatric wards were not studied. Thirdly, the number of patients with CCHF

was smaller than those with dengue. However, we would recommend future studies in this regard, in order to arrive at a better explanation of the epidemiological and clinical data of these febrile illnesses, which are quite common in Pakistan.

CONCLUSION

CCHF causes more deaths than dengue fever. Moreover, CCHF kills more males than females. Contrary to CCHF, dengue related deaths are commoner in females. Increasing age is an indicator of worse prognosis in both. However, platelet count on admission does not influence the final outcome in both CCHF and dengue fever.

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