

A COMPARISON OF CLINICAL DIAGNOSIS AND SEROLOGICAL DIAGNOSIS IN AN EPIDEMIC OF CRIMEAN-CONGO HAEMORRHAGIC FEVER

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ABSTRACT:

Background: Crimean Congo Haemorrhagic Fever (CCHF) is life-threatening disease caused by Nairovirus of genus Bunyavirus caused by tick bite of Hayalomma species or by direct contact of the blood/sera of the patient and animals suffering from this disease. Epidemics have been occurring in Balochistan province of Pakistan and neighbouring Afghanistan and Iran from time to time with high mortality.

Aim: In the absence of facilities for detection of serological markers of CCHF (IgM & IgG antibodies and PCR for viral RNA), a study was designed to diagnose and treat cases of CCHF reporting to a specialist unit hospital situated at Quetta, Pakistan. The aim was to compare the clinical features, complications and outcome of both groups of patients; one detecting the disease clinically only and the other depending upon serological tests for the diagnosis.

Methods: Thirty-four patients having fever of less than two weeks of duration with features of bleeding from the skin and various orifices were included in this study from June 2001 to September 2001 after hospitalization. Index case and some of the consecutive cases were subjected to detection of serological markers. Rest of the cases were diagnosed on clinical grounds and baseline laboratory investigations only. Difference in both the groups was noted carefully. All the patients were given Ribavirin and blood products as and when required.

Results: Statistically there was no obvious difference in clinical manifestations (fever, body aches, purpuric spots, ecchymosis, epistaxis, gum bleed etc.) and laboratory findings (blood picture, serum ALT, serum urea and electrolytes, PT, APTT, etc). There was also no difference in mortality of the two groups studied.

Conclusion: In an ongoing outbreak of CCHF, history, clinical findings and supportive baseline laboratory investigations may be sufficient for early detection and treatment of CCHF cases. However for documentation of start of epidemic, serological markers should be done. Therefore facilities for detection of viral markers of CCHF should be available at centers like Quetta.

KEYWORDS: CCHF, Clinical diagnosis, Lab diagnosis

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INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) was first described in Crimea in 1944 and was hence given the name of Crimean hemorrhagic fever. Congo virus was first isolated in Zaire (Africa) from the blood of a febrile patient in 1956. Linkage of the names of two places gave the current name Crimean-Congo hemorrhagic fever (CCHF)^{1,2}. CCHF is a serious disease with high mortality in humans³. The disease is endemic in Balochistan (Pakistan) where different ecological factors provide opportunities for the virus to stay and thrive. Outbreaks of CCHF were confirmed in 1987, 1994, 1995, 1998, 2000 and in 2001 in various parts of the

province⁴. The CCHF virus has been classified as a Nairovirus in the genus Bunyavirus. Domestic animals like cattle, sheep and goat are commonly the source and reservoir, the animals become infected from the bite of infected tick most commonly the members of Hyalomma genus^{5,6}.

The humans may acquire infection through infected tick bite, during family outbreaks, slaughtering or manipulating the blood of infected animals. Body secretions and blood of patient is infectious and cause nosocomial spread to health care workers and patient attendants. The incubation period in case of tick bite is commonly 1-3 days to the maximum of 9 days. In case of person-to-person spread incubation period is 5-6 days, maximum being 13 days. There is a wide range of symptoms. Commonly sudden onset of high-grade fever, headache, dizziness, flu like symptoms, nausea, abdominal pain, and muscle aches is followed by generalized bleedings and in severe cases vascular collapse and shock⁷. In most of the cases platelet count and absolute neutrophil count fall, absolute lymphocyte count and serum alanine amino transeferase (ALT) are increased. In few cases renal functions are deranged, blood urea and serum creatinin are thus raised. The definite diagnosis of CCHF is performed in specially equipped high biosafety level laboratories. IgM and IgG antibodies are detected in serum by Enzyme linked immunoassay. Patients with fatal disease do not usually develop a measurable antibody response and in these individuals as well as in patients in first few days of illness, diagnosis is achieved by virus detection in blood or tissue samples by polymerase chain reaction (PCR). Facility of both of these investigations is not readily available to clinician treating the CCHF patients in Balochistan, thus a clinician has to rely on his clinical suspicion and supportive investigations to exclude other conditions simulating CCHF. This study is aimed to evaluate the importance of clinical assessment and supportive investigations in early diagnosis of CCHF in an outbreak of this disease in Balochistan in year 2001, without relying upon the serologi-

cal markers (IgM, IgG antibody & PCR for CCHF RNA). These investigations were asked for the index case and some of the consecutive cases only as these investigations were to be sent to National Institute of Virology Johannesburg.

PATIENTS AND METHODS

Patients

The government of Baluchistan established a CCHF treatment center at Fatima Jinnah Hospital Quetta after confirmed reports of death of few cases suffering from illness like CCHF in Pishin District. The doctors, paramedics, health workers and general public were informed about the significance of early detection and treatment of this disease through media, advertisement in local newspapers and with an advice to refer all such cases to the center for free treatment. Thus a prospective and quasi experiment study was undertaken to document the evolution of epidemic, the different aspects of the disease and to document the importance of clinical diagnosis of disease compared to definitive laboratory diagnosis as well as to measure the response to different modalities of treatments. Thus all patients with fever of less than two weeks duration and bleeding manifestations referred to Fatima Jinnah Hospital Quetta were included in the study. A clinical history was carefully obtained and examination was carried out. Patients were divided on the basis of history and clinical examination in two groups i.e. those having classical features were included in the study and those unlikely to be suffering from CCHF and requiring further evaluation /observation before being excluded from the study. These cases were detained in a separate section of the center.

Inclusion criteria:

1. Fever with weakness and fatigue of less than two weeks duration^{2,7}.
2. Unexplained mucous membrane, skin or conjunctival bleeds^{2,7}.
3. Thrombocytopenia with platelet count $<100 \times 10^9 /L$.

Exclusion Criteria

1. Patients with fever and fatigue of less than 02 weeks duration but with obvious features of other diseases like typhoid and having overt causes of bleeding diathesis.
2. Platelet count $>100 \times 10^9$ /L.
3. Detection of Plasmodium falciparum on blood film examination.

Methods

Those patients included in study were kept in isolation and protocol of barrier nursing was enforced⁸. Serial blood samples were obtained for Complete blood counts, serum ALT, bilirubin, urea/creatinine. Sera were sent for viral RNA detection by polymerase chain reaction (PCR) and CCHF specific Immunoglobulin detection (IgG, IgM).⁹⁻¹¹ Blood group determination was carried out and cross-matched blood/ fresh frozen plasma was made available on urgent basis. All diagnosed patients were treated with blood components whenever required and with oral Ribavirin as the injectible Ribavirin was not available. All the contacts were also given oral Ribavirin.

RESULTS

Eighty-four patients were received from June 2001 to October 2001.¹² Thirty nine patients had fever, body aches, and fatigue but revealed no clinical evidence of generalized bleeding. This group also had normal blood counts and

serum ALT and thus was excluded from the study. These patients were shifted to medical ward for further management. Nine patients were detected of having Falciparum Malaria and another two of acute leukemia. These patients were also shifted to medical wards and were excluded from study. Thirty-four patients were diagnosed and treated as definite cases of CCHF. Most of these patients belonged to Northern Balochistan. Twenty-six patients were male and eight patients were female. Age of patients varied from 4-75 years with a mean age of 32 years. These patients presented with varying symptoms as detailed in Table-I. Lab results of initial investigations are shown in Table-II. Antibody titers (IgG and IgM) were tested in all patients and were found positive in only 6. PCR was performed only in 10 patients; it was positive only in three and negative in seven patients. Two of these PCR positive patients were found negative for antibodies i.e., IgG and IgM, whereas one patient tested positive both with PCR as well as IgG and IgM. Four patients were received in a moribund state and expired before treatment could be initiated. Four patients died during treatment. Overall mortality was 23%. In 26 patients, who survived, bleeding stopped on the average in 3 days, whereas other symptoms resolved in four days.

Table-II: Laboratory results (mean)

Table-I: Symptoms of CCHF patients

Symptom	Serologically Proved* n=8	Clinical/Lab suggestive** n=26
Fever	8 (100%)	26(100%)
Body aches	8(100%)	26(100%)
Purpuric spots	8(100%)	26(100%)
Ecchymosis	8(100%)	26(100%)
Epistaxis	8(100%)	26(100%)
Gum bleed	4(50%)	5(19%)
Melena	3(37.5%)	13(50%)
Haematuria	4(50%)	1(4%)

* Serologically proved means IgG/IgM positive and/or PCR positive.

** Clinical and lab suggestive means diagnosed on clinical basis with baseline lab investigations only.

Analyte	Serologically Proved* n=8	Clinical/Lab suggestive** n=26
Bilirubin mmol/L	18	20
ALT U/L	195	323
Urea mmol/L	11.9	7.7
Creatinin umol/L	124	94
Haemoglobin g/dl	10.2	9.7
Platelet count $\times 10^9$ /L	25	22
TLC $\times 10^9$ /L	2.62	4.8
ANC $\times 10^9$ /L	1.01	2.7
ALC $\times 10^9$ /L	1.6	1.9

TLC: Total leukocyte count. ANC: Absolute neutrophil count. ALC: Absolute lymphocyte counts.

* Serologically proved means IgG/IgM positive and/or PCR positive.

** Clinical and lab suggestive means diagnosed on clinical basis and baseline lab investigations only.

DISCUSSION

Sporadic cases of CCHF are being reported in Balochistan since 1978 and epidemics since 1987. Probably disease is present in neighboring Afghanistan since long time but due to lack of epidemiological surveys it remained unreported. In March 2002, 41 deaths from hemorrhagic fever have been reported in eastern Afghanistan¹³. In autumn 2001 there was outbreak of CCHF along the western border of Afghanistan with Iran. The Iranian outbreak included southeastern provinces along Afghanistan's western border and was probably due to illegal movement of animals across the border; about 100 cases were reported¹³. The mortality rate varies. Virus causing CCHF in this region is of high virulence with mortality ranges from 30-75%, however, enough data to support this observation is lacking. The virus is notorious for nosocomial outbreaks, typically following admission of undiagnosed index case to a health care facility where it was not suspected; the mortality rate in such cases is up to 40%¹⁴. It is important to suspect, isolate and treat patient of CCHF as soon as possible. Just missing a single case may lead to spread of disease to family members or may evoke a nosocomial outbreak. The diagnosis of CCHF is based upon viral RNA detection by PCR in blood and secretions of patient. IgM develops in about 5-6 days and is helpful in diagnosis¹⁵. Both of these investigations are expensive, not readily available and practically of little use in early case detection and management. Moreover these investigations may even be negative in a definite patient of CCHF. As concluded from Table-I and Table-II there is no statistically significant difference in different parameters of IgM/PCR proved cases and clinically diagnosed cases having low platelet and low WBC counts with raised serum ALT values in an epidemic of CCHF. Thus, in an epidemic the mainstay of diagnosis should be the clinical suspicion supported by thrombocytopenia, leukocytopenia and raised ALT. The absence of malarial parasite in blood films supports the diagnosis, as Malaria is hyper

endemic in this area. It is a leading cause of disseminated intravascular coagulation and mortality in Balochistan in summers. A history of fever of less than two-week duration, bleeding manifestations in a resident of endemic area with a history of recent contact with CCHF patient or animal is sufficient for suspicion of CCHF. It warrants proper laboratory workup, clinical confirmation and early treatment with Ribavirin, blood products etc. Antibody detection and PCR for viral RNA of CCHF virus may take longer time for confirmation and it is not readily available (as blood samples were sent to National Institute of Virology, Johannesburg) expensive and delays the treatment which is vital and life saving. However, blood samples of index case and some of the initial consecutive cases may be sent for confirmation of the start of the epidemic. Rest of the cases could be treated on clinical grounds only.

CONCLUSION

1. Any patient residing in endemic area, presenting with history of fever of less than two weeks duration, with bleeding in the skin and orifices with other manifestation of viral disease in autumn to summer should arouse suspicion of CCHF and it entitles the patient for isolation/ treatment in a specialized center. Clinical diagnosis of CCHF can safely be made if baseline investigations reveal leucopenia, thrombocytopenia and raised ALT in the absence of some other obvious cause of bleeding.
2. Sera belonging to index case and some of the consequent cases must be submitted for PCR of CCHF viral RNA and or IgM/IgG antibody detection to confirm the outbreak and subsequent patients should be isolated and treated on clinical grounds only. Antibodies may not ever develop even in a classic case of CCHF or may take 5-6 days to develop detectable levels. Collection and transportation of samples be made with utmost care to avoid nosocomial spread of disease. Therefore in an ongoing epidemic it is not necessary that confirmation of

disease should be made in every case by serological examination; early clinical diagnosis is enough.

3. The samples are sent to National Institute of Virology, Johannesburg through the courier. It is recommended that facilities of these tests should be made available in referral centers like the one made at Quetta, Balochistan. Existence of such centers should be the responsibility of the government in collaboration with National Institute of Health.
4. Further similar observations will fortify our recommendation of diagnosis on clinical basis, especially during epidemics of CCHF, when the serological diagnostic facilities are barely available.

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