Crimean Congo Hemorrhagic Fever: Requires Vigilance and Not Panic

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Abstract
Crimean Congo hemorrhagic fever (CCHF) has been in the news with reports of its outbreak in India from Gujarat. CCHF is caused by a virus which is a member of the Nairovirus genus of the family Bunyaviridae. All of these viruses are transmitted by either ixodid or argasid ticks. Humans get this infection after a bite of an infected tick or from one infected human to another by contact with infectious blood or body fluids. Workers in livestock and agriculture industry, slaughterhouses, and veterinary practice are most prone to this infection. In severe cases after 3-6 days of the onset of symptoms hemorrhagic manifestations occur. IgG and IgM antibodies may be detected in serum by ELISA from about the sixth day of the illness. The mainstay of treatment in CCHF is supportive. Management of DIC, sepsis, shock and MODS should be undertaken. The antiviral drug Ribavirin has shown benefits. Benefits of treatment with ribavirin outweigh the fatal risks, and ribavirin may therefore be recommended. People at risk should use effective personal protective measures against tick bites. Acaricide treatment of livestock in CCHF virus endemic areas is effective in reducing the population of infected ticks.

Introduction

Crimean Congo hemorrhagic fever (CCHF) has recently been in the news with first ever reports of its outbreak in India from the village of Kolat which is 30 Kms southwest of Ahmedabad in Gujarat. A 30 year old woman and a doctor and nurse treating her in Ahmedabad succumbed to this illness creating panic in the local population and the country as well. General public including the medical fraternity was not fully aware of this disease, thus a fear of unknown was spread initially.

Historical Background

CCHF like symptoms affecting people were described initially by physicians in 12th century from the region currently known as Tazhikistan. It was described as a clinical entity in 1944-1945 when 200 Soviet military personnel were infected in war affected Crimea. Similar disease affected the population in Congo and Uganda in 1967, thus the name Crimean Congo hemorrhagic fever. In 1967, a breakthrough in CCHF research came when Chumakov and his colleagues at the Institute of Poliomyelitis and Viral Encephalitides in Moscow first used newborn white mice for the isolation of CCHF virus. This resulted in a Drosdov strain which became the prototype strain for experimental work.4

The Etiological Agent

CCHF as mentioned before is caused by a virus. This virus is a member of the Nairovirus genus of the family Bunyaviridae, Hantavirus also belongs to the same family. Nairovirus genus contains 7 species of virus with 34 strains reported till date. All of these viruses are transmitted by either ixodid or argasid ticks (i.e., hard or soft ticks, respectively). Structurally the CCHF virus is an RNA virus, it is spherical, approximately 100 nm in diameter, and has a host cell-derived lipid bilayered envelope approximately 5–7 nm thick, through which protrude 8–10 nm in long glycoprotein spikes.5

Epidemiology of CCHF Virus

Like other tick-borne zoonotic agents, CCHF virus generally circulates in nature unnoticed in an enzootic tick–vertebrate–tick cycle. CCHF virus has been isolated from numerous domestic and wild vertebrates, including cattle, goats, sheep, hares, hedgehogs, a Mastomys spp. mouse and even domestic dogs. Antibodies to CCHF virus have also been reported in domestic cattle, horses, donkeys, and pigs from various parts of Europe, Asia, and Africa. Birds are observed to be refractory to CCHF virus infection. Vertebrates serve as a source of blood for the ticks. Ticks of the genus Hyalomma specifically act as vector for the CCHF virus. CCHF viral replication and tissue tropism in Hyalomma truncatum ticks were examined by Dickson and Turell in 1992.6 Although Hyalomma spp. ticks are considered the most important in the epidemiology of CCHF, the virus has been isolated from ticks in other genera (i.e., Rhipicephalus, Boophilus, Dermacentor, and Ixodes spp.) as well, which may contribute to its wide geographical distribution. Ticks not only are the vectors for CCHF virus but they act as reservoirs as well. The virus can be passed directly from immature ticks to their subsequent life stages.

Geographically this tick borne viral infection has been reported from different countries in Africa, Asia, Southeast Europe and Middle East. Outbreaks of CCHF have recently been reported in Iran in 2002, in Turkey in 2004 and in Pakistan in 2010.79

Clinical Features

Humans get this infection after a bite of an infected tick or contact with infected blood of animals. CCHF can be transmitted from one infected human to another by contact with infectious blood or body fluids. Most of the human cases are workers in livestock and agriculture industry, slaughterhouses, and...
veterinary practice. Documented spread of CCHF has also occurred in hospitals due to improper sterilization of medical equipment, reuse of injection needles, and contamination of medical supplies. Nosocomial transmission have been reported from Pakistan, Iraq, United Arab Emirates, South Africa, Sudan and Iran. Human infection with CCHF virus leads to predominantly a severe hemorrhagic disease.

Course of this disease follows four distinct phases in humans namely incubation phase, prehemorrhagic phase, hemorrhagic phase and convalescence phase. However the duration and manifestations during these phases may vary from patient to patient.

The incubation period after the tick bite can be as low as 1-3 days to as long as 7-8 days. This depends on the route of exposure to virulence and viral dose.

After the incubation period, the prehemorrhagic phase is characterized by a sudden onset of fever, chills, severe headache, myalgias, rash, arthralgias, dizziness, photophobia, back and abdominal pains. Additional symptoms such as nausea, vomiting, diarrhea and an accompanying loss of appetite are common. Fever can be as high as 39-41°C. Neuropsychiatric manifestations like violent behavior, psychosis, change in mood and confusion etc. have also been reported. Other features which have been observed include cardiovascular features like bradycardia and hypotension.

In severe cases after 3-6 days of the onset of symptoms hemorrhagic manifestations occur. The spectrum of hemorrhages varies from petechiae to ecchymoses over skin and mucous membranes. Red eyes, flushing of face, throat congestion and petechiae over palate can be observed. Bleeding can present as epistaxis or dark coffee-colored vomitus due to hematemia or tar-colored stools i.e. melena or hematuria. Bleeding from other sites like vagina, gum bleeds and intracerebral bleeds have also been reported. Patients can develop jaundice, hypovolemic shock, disseminated intravascular coagulation (DIC), prerenal failure and in severe cases can develop multiorgan dysfunction syndrome (MODS).

Patients who survive this phase, the convalescence period begins about 15-20 days after onset of illness. It is generally characterized by prolonged and pronounced generalized weakness, weak pulse, and sometimes complete loss of hair. Sequelae include polyneuritis, headache, dizziness, poor appetite, poor vision, loss of hearing, and loss of memory. These are rarely permanent, but may persist for a year or more.

**Laboratory Findings**

These include anemia, leucopenia, and thrombocytopenia, increased AST/ALT levels, prolonged bleeding time, prothrombin time (PT), and activated partial thromboplastin time (PTT), elevated fibrin degradation products (FDPs), and decreased fibrinogen. Urinalysis may reveal proteinuria and hematuria, and patients may develop oliguria and azotemia. Elevated lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) is also observed.

**Pathogenesis**

Pathogenesis is not completely understood as there are limited studies done on CCHF. This scarcity of experimental work is due to the requirement of biosafety level IV labs to conduct studies on CCHF. Such laboratories have limited availability. A common pathogenic feature of hemorrhagic fever viruses is their ability to disable the host immune response by attacking and manipulating the cells that initiate the antiviral response. Capillary fragility is a common feature of CCHF, suggesting infection of the endothelium. Endothelial damage accounts for the characteristic rash and contribute to haemostatic failure by stimulating platelet aggregation and degranulation, with consequent activation of the intrinsic coagulation cascade. Reactive hemophagocytosis have been reported from studies in Turkey which suggested that cytopenias observed during CCHF infection could be attributed to it. Proinflammatory cytokines like IL-1, IL-6, and TNF-alpha also contribute in pathogenesis and mortality.

**Differential Diagnosis**

There are a number of tropical infections which presents similar clinical features and hence they should be suspected and ruled out while making a diagnosis of CCHF. The differentials include falciparum malaria, leptospirosis, dengue hemorrhagic fever, typhoid fever, septicemic plague, rickettsial infections, meningococcemia, viral hepatitis and other viral hemorrhagic fevers.

**Laboratory Diagnosis**

Methods of diagnosis include detection of antibodies to viral antigen by enzyme-linked immunosorbent assay (ELISA), virus isolation, antigen detection and polymerase chain reaction (PCR).

IgG and IgM antibodies may be detected in serum by ELISA from about the sixth day of the illness. Either the presence of IgM or a 4-fold rise in the titer of IgG antibody in serum samples between the acute and convalesce phases is diagnostic of the disease. Thus ELISA test may not be helpful in initial days of infection when the antibody levels are low. In the initial stages virus may be isolated from blood or tissue specimens and grown in cell culture, but virus isolation is of limited value because it requires a biosafety level 4 (BSL-4) laboratory, which is not available in most endemic areas.

More recently, PCR, a molecular method for detecting the viral genome, has been successfully applied in the diagnosis of viral hemorrhagic fevers. Chinikar et al found few cases with positive RT-PCR among those whose illness had been confirmed by serology. Viral antigen detection by ELISA and RT-PCR is the most useful diagnostic technique in the acute clinical setting. Diagnosis should be based initially on clinical findings, and laboratory tests be used to confirm or exclude it.

**Treatment**

The mainstay of treatment in CCHF is supportive in nature with careful maintenance of fluid and electrolyte balance, circulatory volume, and blood pressure. Management of DIC, sepsis, shock and MODS based on the established guidelines should be undertaken. Treatment options specific to the disease are limited. There have been reports of possible benefits with treatment of patients using serum prepared from the blood of recovered CCHF patients or gammaglobulin obtained from immunization of horses.

Recently immunotherapy has also been attempted via passive transfer of CCHF survivor convalescent plasma. But these results are based on uncontrolled experiments and definitive evidence regarding their effectiveness is lacking.

The antiviral drug Ribavirin has shown benefits in in-vitro studies although it has not been approved by US FDA for
its use in CCHF patients. There have been case reports of Ribavirin being used in these patients with patients showing some benefit. This antiviral agent has a broad spectrum of activity in vitro against RNA viruses. Clinical efficacy has been demonstrated with Ribavirin for the treatment of infections caused by hemorrhagic fever viruses (with oral and intravenous formulations of ribavirin). A systematic review and meta-analysis on the use of Ribavirin for CCHF concluded that there was no clear message of benefit available from the current data on ribavirin as observational data are heavily confounded, and their exists only one randomized controlled trial (RCT) which has limited power. Thus, ribavirin could potentially have benefits in this condition although there is a need for a good quality RCT to make definitive conclusions. The dosage recommended by the World Health Organization (WHO) of Ribavirin is 30 mg/kg as an initial loading dose, then 15 mg/kg every 6 h for 4 days, and then 7.5 mg/kg every 8 h for 6 days.

Currently in Indian markets Ribavirin is only available in oral form with tablet strength of 200 mgs, if it is considered for use the approximate cost of 10 day therapy with this drug would currently be around Rs 6000/- for each patient with an average weight of 50 Kg. The drug is advised to be administered within 24 hours of hospital admission for better results.

In the context of Viral Hemorrhagic Fevers of unknown cause, it is believed that the benefits of treatment with ribavirin outweigh the fatal risks, and ribavirin is therefore recommended. Ribavirin is contraindicated in pregnancy and its use in children has not been approved by FDA. The important side effect of this drug which should be monitored includes anemia which is reversible and this usually does not requires transfusion.

A newly identified molecule known as MxA, a member of the interferon-induced GTPases that belong to the dynamin superfamily prevented replication of CCHF viral RNA when presented intracellularly and inhibited production of new infectious virus particles by interacting with a component of the nucleocapsid. This agent is still in experimental stage.

**Prognosis**

Various studies have reported case-fatality rate from 15% to 70%. Hemorrhagic manifestations, confusion, and laboratory evidence of marked elevation of AST, ALT, GGT, CPK, LDH, frank DIC, thrombocytopenia, splenomegaly are predictors of fatal outcome.

**Prevention and Control**

Groups of individuals who are considered to be at risk of contracting CCHF virus like animal handlers, abattoir workers, and veterinarians should use effective personal protective measures against tick bites. However, acaricide treatment of livestock in CCHFV endemic areas is effective in reducing the population of infected ticks.

Permethrin-impregnated clothing should be used, trousers should be tucked into boots or socks, light-colored clothing should be worn to facilitate tick identification with use of insect repellants on exposed skin, and daily skin inspection for ticks are essential for prevention.

Other groups who are at risk include those caring for CCHF patients. In fact, the risk of nosocomial infection in health-care workers is well documented and can be extremely high, especially during the hemorrhagic period of disease.

Laboratory workers handling viral material are also at high risk of contracting the disease. CCHF thus has been classified as biosafety level 4, category A or B pathogen which could potentially be a bioterrorism tool. Thus universal precautions should be observed in the patient-care areas and the laboratory.

The suspected patient should be placed in isolation, those entering the patient’s room should wear gloves and gowns, and those approaching within one meter should wear face shields or surgical masks and eye protection to prevent contact with blood or other body fluids.

**Postexposure Prophylaxis**

Postexposure prophylaxis should be considered potentially for those exposed to hemorrhagic fever viruses (including CCHFV) in a bioterroristic attack and all known high-risk individuals such as those who have mucous membrane contact (kissing or sexual contact with a patient) or have percutaneous injury in contact with the patients’ secretions, excretions, or blood. Prophylaxis should also be considered for those with close contacts such as living or shaking hands with the patients and those who process laboratory specimens. Such people are placed under medical surveillance and made to observe themselves with temperature monitoring twice daily. If a temperature of 38.3°C or higher develops, treatment with ribavirin should be initiated promptly as presumptive treatment of CCHF. The dose for PEP recommended is oral Ribavirin 200 mgs twice daily for 5 days.

**Summary**

In the current scenario Health Department, Government of India, is taking relevant measures to control the tick infestation in Gujarat. Other areas have also started surveillance. At physician level it is recommended that CCHF should be considered in those patients having:

- Compatible clinical manifestations
- Epidemiological risk factors
- Travel to or staying in endemic area for CCHF
- Contact with suspected cases of CCHF, or contact with animals
- Compatible laboratory findings like a platelet count of <150,000/mm² and a WBC count of <3000 or >9000 /mm
- Rule out other common differentials like dengue hemorrhagic fever.

Such patient’s serum should be sent for investigation to reference laboratories equipped to handle CCHF, like NIV, Pune in India. Patient should be managed in isolation with strict universal precautions followed by the physicians. Treating physician should also report the cases to the concerned authorities for surveillance.

**References**


