CRIMEAN CONGO HEMORRHAGIC FEVER: AN EMERGING TICK-BORNE DISEASE

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Abstract

Crimean Congo hemorrhagic fever (CCHF) has the most extensive geographic distribution of the medically significant tick-borne viruses. Its causative agent is a negative-sense, single-stranded RNA virus belonging to the family *Bunyaviridae*, genus *Nairovirus*. The virus can be transmitted mainly through direct contact with blood or tissues from infected livestock or through bites of *Hyalomma* ticks. Moreover, nosocomial and community outbreaks have been already described. Although in Greece serologic evidence of the virus has been observed, no case of CCHF has been reported until 2008; however, on June 2008 a case of CCHF was reported in Greece and phylogenetic analysis showed that the causative agent of CCHF was a virus strain similar to other strains detected or isolated in the Balkan Peninsula, Russia and Turkey which are associated with severe and sometimes fatal disease in humans. This case identification raised many concerns on the emerging potential and the changing epidemiology of CCHF. The present article reviews on the epidemiological and clinical features of CCHF; moreover, prevention and control strategies are being described in detail.

Keywords: Crimean Congo Hemorrhagic Fever, epidemiology, prevention

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Introduction

Crimean Congo hemorrhagic fever (CCHF) was first described in the 12th century as a hemorrhagic syndrome in present day Tajikistan [Ergönül, 2006]. During that era, it was speculated that the disease's transmission was associated to louse or ticks that normally parasite black birds. However, in the modern era, the first outbreak of the CCHF was reported in 1944-1945 in the Crimea region when more than 200 cases occurred and at that time the disease was called Crimean Hemorrhagic Fever. Ten years later and specifically in 1956, the virus was isolated from a febrile

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patient in Belgian Congo and this isolate was noted to have the same antigenic structure with the Crimean strains. For this reason, the virus was called Crimean Congo Hemorrhagic Fever [Simpson et al., 1967; Ergönül, 2006]. Nowadays, outbreaks of CCHF have been documented in Africa, the Middle East, Eastern Europe, and Western Asia [Hoogstraal, 1979].

CCHF is a severe hemorrhagic fever with a case fatality rate of up to 50%. The virus that causes the disease is a tick-borne virus belonging to the family Bunyaviridae, genus Nairovirus [Donets et al., 1977; Ellis et al., 1981; Martin et al., 1985]. Like other nairoviruses, CCHF virus is an enveloped single stranded negative-sense RNA virus and its tripartite genome consists of a small (S), a medium (M) and large (L) segment which encode for the nucleocapsid protein (NP), the envelope glycoproteins G1 and G2 and an RNA-dependent polymerase, respectively [Marriott et al., 1992; Marriott et al., 1994]. The virus is transmitted to humans through the bite of infected ticks or by direct contact with viremic animals or humans [Camicas et al., 1994; Ergönül, 2006]. Infected humans can spread the disease via close contacts which may result in community outbreaks and nosocomial infections [Burney et al., 1980; van Eeden et al., 1985; Mardani, 2001; Jamil et al., 2005]. The potential human to human transmission along with the high mortality rates, the fears that the virus could be used as a bioterrorism agent and the increase of the incidence and geographic range of the Crimean Congo hemorrhagic fever make the virus an important human pathogen. In this review, the epidemiological and clinical features of Crimean-Congo hemorrhagic fever are being described in detail. Moreover, prevention and control strategies are being discussed in order to reduce the risk of the disease transmission.

Disease Transmission, Epidemiological and Clinical Features

Like other tick borne zoonotic agents, CCHF virus circulates in nature in an enzootic tick-vertebrate-tick cycle. Humans are being infected mainly through direct contact with blood or tissues from infected livestock or through tick bites. CCHF virus is transmitted by *Hyalomma* genus ticks and in particular by *Hyalomma marginatum marginatum.* Ticks of the genus *Hyalomma* serve indeed as vectors and reservoir of the CCHF virus and the geographic distribution of the disease coincide with the global distribution of *Hyalomma* ticks [Charrel et al., 2004; Whitehouse, 2004; Vorou et al., 2007]. The virus is reported in over than 30 countries in Africa (Democratic Republic of Congo, Uganda, Mauritania, Nigeria, S. Africa, Senegal, ect), Southeast Europe (Russia, Bulgaria, Kosovo, Turkey, Greece, ect), the Middle East (Iraq, Iran, Saudi Arabia, Oman) and Asia (China, Kazakhstan, Tajikistan, Uzbekistan, Pakistan) [Morikawa et al., 2007; Koutis, 2007]. In this regard, the geographical distribution of CCHF virus is the greatest among all tick-borne viruses. CCHF virus has been isolated from adult *Hyalomma* genus ticks in the '60s and transovarial and transstadial transmissions have been already suggested since viral isolates have been also found in field collected eggs and unfed immature stages of *H. marginatum*, respectively [Watts et al., 1988]. CCHF virus has been also isolated in laboratory from other tick genera eg. *Rhipicephalus, Ornithoros, Boophilus, Dermacentor* and *Ixodes spp.*

Although, the virus persists in ticks, vertebrates are needed to provide blood meals for the ticks and a variety of livestock can become infected with the CCHF virus. In fact, numerous domestic and wild vertebrates have been reported to present antibody response and/or viremia [Vorou et al., 2007]. This livestock includes cattle, goats, sheep, horses, pigs hares, ostriches, camels, donkeys, mice and domestic dogs. In contrast to human infections the livestock's infections generally result in unapparent or subclinical disease [Swanepoel et al., 1987; Logan et al., 1989; Shepherd et al., 1991; El-Azazy et al., 1997; Whitehouse, 2004; Nabeth et al., 2004]. However, the infected livestock during the viremic phase is dangerous for the disease transmission in humans. In this regard, domestic ruminant animals such as cattle, sheep and goats will

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present viremia for one week after becoming infected [Athar et al., 2003]. Although it has been shown that the majority of birds is resistant to infection [Whitehouse, 2004] the potential role of migratory birds in the disease dissemination could not be ignored. Migratory birds could carry infected ticks and could be implicated in the CCHF virus spread and this was the case of the 2002 outbreak in Turkey which was attributed to the birds' migration from the Balkans [Karti et al., 2004]. On the other hand, the potential role of livestock migration or importation from endemic to non endemic areas has been studied. For instance, the outbreak of CCHF in Pakistan in 2000 coincided with the movement of sacrificial animals from rural to urban areas for the festival of Eid-ul-Azha [Jamil et al., 2005].

Seasonal variations of the disease have been already described. For instance, the highest incidence of the disease has been reported in Pakistan between March and May and again between August and October [Sheikh et al., 2005], whereas in Iran the disease was most common in August and September [Mardani et al., 2003]. This incidence increase was mainly attributed in climatic conditions changes that facilitated tick reproduction [Estrada-Pena, 2001; Gubler et al., 2001]. At this point global warming should be considered in the potential changing epidemiology of CCHF. Specifically, it has been suggested that global warming and climate changes in general may increase the incidence and the geographic range of Crimean-Congo hemorrhagic fever. Global warming may change the epidemiological behaviour of CCHF and in particular it may create a great problem in CCHF prevalent areas by altering the ticks' growth patterns, as well as in areas free of CCHF, by redirecting the migration routes of birds - which host the affected ticks- to areas newly warmed by earth's altered temperature patterns [Purnak et al., 2007]. In particular, although in Greece, serologic evidence of human infection with CCHF virus has been already observed since 1982 [Antoniadis et al., 1982] no case of CCHF has been reported and this was mainly attributed to the different non-pathogenic virus strain A92, isolated in Greece. The genetic divergence between the A92 strain from Greece and strains from the endemic areas from the Balkan peninsula was most likely attributed to the different vectors (*Rhipicephalus bursa* in Greece versus *Hyalomma marginatum* in other European countries) and to the extended mountains separating Greece from other Balkan countries [Papa et al., 2004]. Nevertheless, on June 2008 a case of CCHF was reported in Greece and phylogenetic analysis showed that the causative agent CCHF virus strain was similar to other strains detected or isolated in the Balkan Peninsula, Russia and Turkey which are associated with severe and sometimes fatal disease in humans [Papa et al., 2008]. Whether climatic and environmental changes played any role in providing the favorable conditions for CCHF emergence in Greece have to be further investigated.

As mentioned earlier, humans can be infected incidentally by the bite of an infected tick or via aerosol generated from infected animals' excreta. Infected humans can spread the disease via close contacts and this may result in community and nosocomial outbreaks. Nosocomial outbreaks have been reported in several areas of the world including Bulgaria, Pakistan, Iraq, Dubai, Turkey [Ergönül et al., 2006]. In reality, nosocomial outbreaks coincide with the activity of the CCHF virus within the respective local communities and in the general population [Burney et al., 1980; Suleiman et al., 1980; Swanepoel et al., 1987; Altaf et al., 1998;]. Nevertheless, health care workers are one of the major risk groups for CCHF virus acquisition, when caring for patients with haemorrhages from the nose mouth, gums, vagina and injection sites. The most dangerous conditions for acquiring CCHF virus in the nosocomial setting are interventions for controlling gastrointestinal bleedings and emergency operations in patients who have not been diagnosed with CCHF virus before the operation [Shepherd et al., 1985].
Another group at risk for acquisition of CCHF virus in endemic areas are some

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occupational groups that come in close contact with the infected livestock. These occupational high risk groups include farmers, livestock owners, abattoir workers and veterinarians [Karti et al., 2004; Swanepoel et al., 1985; Ergönül et al., 2004; Bakir et al., 2005]. In these occupational groups, infection usually takes place while slaughtering animals. In such a case, the viremic blood from the infected animal is the most likely source of infection but exposure to ticks during the slaughtering process could not be excluded [Fisher-Hoch et al., 1992]. Several outbreaks have been reported in agricultural workers in Southeast Europe (Bulgaria, Albania, Kosovo and Turkey) [Hoogstraal et al., 1979; Papa et al., 2002a; Papa et al., 2002b; Papa et al., 2004], in Asia (China, Kazakhstan, Tajikistan and Pakistan) [Hoogstraal et al., 1979; Papa et al., 2002c; Smego et al., 2004], in Middle East (United Arab Emirates, Iraq, Saudi Arabia, Oman, Iran) [Al-Tikriti et al., 1981; El-Azazy et al., 1997; Schwarz et al., 1997; Williams et al., 2000; Mardani et al., 2003] and in Africa (Mauritania, South Africa and Kenya) [Watts et al., 1988; Dunster et al., 2002]. Consuming meat is not a risk factor for the disease transmission since the post-slaughter acidification of the tissues inactivates the virus [Ergönül, 2006]. Other recreational activities such as hiking, camping and other rural activities in endemic for CCHF areas have been proposed as risk factors for tick exposure and for disease acquisition [Ergönül, 2006].

CCHF shares many clinical features with other types of viral hemorrhagic fevers. The typical course of CCHF infection in humans has four distinct phases: incubation, prehemorrhagic, hemorrhagic and convalescence period. The incubation period of the virus ranges from 2 to 9 days [Swanepoel et al., 1989] and depends on host, route of exposure and viral inoculum; in this regard, in a study conducted in South Africa it has been estimated that the time to onset of the disease was 3.2 days after tick-bite, 5 days after contact with infected livestock blood or tissue, and 5.6 days after contact with infected human blood [Swanepoel et al., 1987]. The prehemorrhagic period is characterized by sudden onset of fever (39-41^{o}C), rigor, severe headache, photophobia, hypotension, relative brachycardia, tachypnea, nausea and abdominal pain. Symptoms of the gastrointestinal tract may also present. Most cases are associated with cutaneous flushing or rash [Hoogstraal, 1979; Vorou et al., 2007]. The hemorrhagic period is short usually lasts 2-3 days and is characterized by haemorrhage from various sites such as the gastrointestinal, genital-urinary, respiratory tracts and the brain. Skin hemorrhagic manifestations, mucous membrane and conjunctival haemorrhage, may also present [Mardani et al., 2007; Vorou et al., 2007]. The convalescence period begins in survivors 10-20 days after the onset of illness and during this period tachycardia, polyneuritis, temporary complete hair loss, xerostomia, poor vision, loss of appetite, poor vision, loss of hearing and loss of memory may present. Hepatomegaly and splenomegaly have been reported to occur in one third of patients. There is no known relapse of the infection [Whitehouse et al., 2004; Ergönül, 2006; Vorou et al., 2007; Mardani et al., 2007]. Laboratory abnormalities may include leucopenia, thrombocytopenia, and raised levels of aspartate aminotransferase and alanine aminotransferase, lactate dehydrogenase and creatinine phosphokinase. Prothrombin time and activated partial thromboplastin time are prolonged and fibrogen is decreased, whereas fibrin degradation products are elevated [Watts et al., 1988; Swanepoel et al., 1989; Schwarz et al., 1997].

Early diagnosis is essential in terms of case management and prevention of nosocomial and community outbreaks. Differential diagnosis should also be considered for other diseases showing similar symptoms that could be bacterial, viral and other non-infectious diseases [Ergönül, 2006]. CCHF should be considered in those patients having: compatible clinical manifestations (eg. Fever, myalgias and bleeding), epidemiological risk factors (such as tick bite, exposure to infected livestock, crushing a tick between two exposed body parts, contact with suspected cases of CCHF,

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outdoor activities in endemic areas), travel or be residents in endemic areas and compatible laboratory findings (low platelet and high white blood cell count, raised levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and creatinine phosphokinase) [Mardani et al., 2007]. Laboratory diagnosis of suspected CCHF is performed in specially-equipped, high biosafety (biosafety level 4) laboratories. Methods of laboratory diagnosis include antibody detection using enzyme linked immunosorbent assays (ELISA), virus isolation and molecular methods. IgG and IgM antibodies are detected in serum by ELISA or enzyme linked immunoassay (EIA) from about 7 days after the onset of disease [Shepherd et al., 1989]. Specific IgM declines to undetectable levels by 4 months post-infection whereas IgG remains detectable for years. CCHF can be isolated from blood or tissue specimens grown in cell culture during the first five days of illness (WHO, 2001). Viral antigens may sometimes been shown in tissue samples using immunofluorescence or EIA. The virus isolation methods are being used in patients with fatal disease since these subjects do not usually develop a measurable antibody response. The method of choice of rapid laboratory diagnosis is the reverse transcriptase polymerase chain reaction (RT-PCR) which is sensitive, specific and rapid [Drosten et al., 2003].

As far as treatment of CCHF cases is concerned, since there is no drug approved by the FDA, supportive therapy of the patient is highly recommended. Intensive monitoring to guide volume and blood component replacement is required [WHO, 2001]. Even though no drug is approved, the antiviral drug ribavirin has apparent benefits. Its efficacy for CCFH treatment can not be established given the fact that no controlled studies have been performed; however, ribavirin efficacy has been shown in vitro studies [Watts et al., 1989; Paragas et al., 2004], in mice animal models [Tignor et al., 1993] and treatment with ribavirin was shown to be effective in CCHF patients [Fisher-Hoch et al., 1995; Mardani et al., 2003; Ergönül et al., 2004; Ozkurt et al., 2006].

Prevention and control strategies

Although an inactivated, mouse brain derived, vaccine against CCHF virus has been developed, there is currently no effective vaccine available for human use. The aforementioned vaccine was used in 1974 during an immunization programme applied to medical workers and military personnel in CCHF endemic areas [Ergönül, 2006]. After the programme introduction, the incidence rates and the case fatality rates of the disease were both reduced. However, the vaccine could not be applicable in many countries due to its method of preparation.

At present, there are few preventive measures for CCHF that mainly consist on personal protection against tick bites and limitation of exposure to infected livestock or humans. In this regard, persons living or travelling in endemic areas should use personal protective measures that include the avoidance of areas where ticks are abundant and predominantly when the tick vector population is particularly active [WHO, 2001]; to minimize tick exposure light-colored clothing –that facilitates tick identification- and covers legs and arms is recommended. On the other hand, the regular examination of clothing and skin for ticks, the application of tick repellent diethyltoluamide to the skin or permethrin to the clothing are mainstays of prevention [CDC, 1995; WHO, 2001]. Acarides (chemicals intended to kill the tick vectors) in the livestock production facilities is another measure of protection. Acarides can be used on animals before slaughter or export; human outbreaks have occurred after exposure to infected ostriches during slaughter; these infections seem to be preventable by keeping the birds free of ticks 14 days before slaughter. In endemic for CCHF virus it has been suggested to subject the ostriches to a 30-day quarantine period before slaughter. Persons who work with livestock (butchers, farmers, veterinarians) in the endemic areas should take practical measures to protect themselves; these include the use of

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repellents and on the skin and clothing, the use of gloves or other clothing to prevent skin contact with the infected tissue or blood [Chin, 2000;WHO, 2001].

Suspected or diagnosed patient with CCHF should be isolated in a private room, preferably in a negative-pressure room; the subjects should be treated and cared for using barrier-nursing techniques that include disposable gloves, masks, shoe covers and goggles [NIH, 2002]. The patient should be attended only by designated medical/para-medical staff and all used material such as syringes, gloves, tubing ect, should be collected in autoclave-able bag and autoclaved before incinerating. All instruments should autoclaved before re-use and all surfaces should be decontaminated with liquid bleach. The patients' samples should be collected, labelled, sealed and decontaminated from outside with liquid bleach and packed in triple container packing. After the patient is discharged, all room surfaces should be treated with liquid bleach and the room should be fumigated. By using these measures transmission in the nosocomial setting could be prevented [CDC, 1998]. In case of death of the CCHF patient, the dead body should be sprayed with 1:10 liquid bleach solution and then placed in a plastic bag which should be sealed with adhesive tape and the vehicle used for the body's transportation should be disinfected with 1:10 liquid bleach solution. The clothing of the deceased should be burned [CDC, 1998].
In case of direct contact with the patient's blood or secretions the recommended procedure is the rigorous daily follow up of the person that came in contact by checking white blood cell counts and biochemical tests for at least 14 days after exposure and the administration of oral high-dose ribavirin. In this regard, prophylactic ribavirin was administrated in a health care worker who had a needle-stick injury and it has been shown that the subject did not develop CCHF [Smego et al., 2004].

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