Investigation of Crimean-Congo Hemorrhagic Fever Virus Transmission from Patients to Relatives: A Prospective Contact Tracing Study

Mustafa Gokhan Gozel,* Mehmet Bakir, Atifet Yasemin Oztop, Aynur Engin, Ilyas Dokmetas, and Nazif Elaldi

Department of Infectious Diseases and Clinical Microbiology, Cumhuriyet University Medical School, Sivas, Turkey;

Department of Medical Microbiology, Cumhuriyet University Medical School, Sivas, Turkey

Abstract. We investigated the possibility of transmission of Crimean-Congo hemorrhagic fever (CCHF) virus through respiratory and physical contact. In this prospective study, we traced 116 close relatives of confirmed CCHF cases who were in close contact with the patients during the acute phase of the infection and evaluated the type of contact between patients and their relatives. These relatives were followed for clinical signs or symptoms indicative of CCHF disease, blood samples of those with and without clinical signs were analyzed for CCHF virus immunoglobulin M and G (IgM and IgG, respectively) by enzyme-linked immunosorbent assay. No close relatives developed any signs or symptoms of CCHF and were negative for CCHF virus IgM and IgG. The results suggest that CCHF virus is not easily transmitted from person to person through respiratory or physical contact.

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne disease caused by CCHF virus (CCHFV), which belongs to the *Bunyaviridae* family, and *Nairovirus* genus.^{1,2} Human infections begin with nonspecific febrile symptoms but progress to a serious hemorrhagic disease. In severe cases, circulatory shock and disseminated intravascular coagulation may occur and result in death.^{3–6} The fatality rate attributed to this infection is between 3% and 30%.^{4,5,7,8}

The CCHFV is generally transmitted to humans through the bite of *Ixodid* ticks or by contact with blood or tissue of infected livestock.^{3,5} Human-to-human transmission has been reported only by direct contact with viremic patients during the acute phase of infection. Needle stick injuries, gastrointestinal hemorrhage interventions, emergency surgical procedures, and unsafe handling of patients or their infected materials have been reported to be high-risk activities for CCHFV transmission; however, transmission through droplet, viral droplet, or physical contact has not been definitely tested.^{9–14} Moreover, transmission may occur by respiratory contact.¹ We conducted a prospective contact tracing study to investigate the possibility of CCHFV transmission through respiratory contact, including droplet and airborne, and ungloved physical contact with the patient or objects around the patient.

This study was conducted at the Cumhuriyet University Hospital in Turkey, between June and September 2011. The CCHF patients were generally referred to our hospital 2–5 days after the initial onset of disease symptoms. This delay was primarily because of non-specific symptoms on the first several days of the infection. After confirmation of CCHF infection, the first degree relatives from the same household were identified and types of repeated contact between patients and their relatives were recorded. Some of these relatives were allowed to remain in the same hospital room as caregivers, because many patients and their relatives came from outside the city, had strong emotional ties and fear of death, and the relatives desired to be near the patients during what might be their last days; however, the use of protective measures (i.e., gloves, gown, and masks) when handling patients and their wastes was explained to all the patients' relatives.

Data collection consisted of a face-to-face interview questionnaire. An interviewer explained the study purposes to relatives on admission and obtained their informed consent. The relatives who did not meet requirements of the study were excluded. The demographic characteristics of close relatives are shown in Table 1. In addition, the degree of kinship and the type of patient contacts were recorded and are shown in Table 2. The first blood sample was taken on the patient's day of admission. All relatives were followed for clinical signs indicative of infection with CCHFV, and a second blood sample was taken at least 14 days after the last contact.

Patient serum samples from acute and convalescent phases of CCHF were sent to the Virology Laboratory at the Refik Saydam Hygiene Center in Ankara, Turkey. Patients whose serum samples were positive for CCHFV RNA by reverse transcriptase-polymerase chain reaction and/or CCHFV-specific immunoglobulin M (IgM) by enzyme-linked immunosorbent assay (ELISA) in blood were defined as confirmed CCHF cases.

The first and second blood serum samples of relatives were tested for CCHFV-IgM and IgG by commercial ELISA kits (Vectocrimean-CHF-IgM and IgG, Vector-best, Koltsovo, Novosibirsk, Russia) according to manufacturers' directions in the University's Department of Medical Microbiology.

The study was approved by the Medical Ethics Committee of Cumhuriyet University. We used the Statistical Package for the Social Sciences (SPSS) version 14 for Windows (SPSS Inc., Chicago, IL) for statistical analyses. Parametric data were expressed as mean $\pm$ SD and categorical data as percentages. Proportions for categorical variables were compared using the χ^2 test. A *P* value of < 0.05 was considered significant.

One hundred thirty-two relatives of 90 confirmed CCHF cases were initially included in the study. Two patients died and 88 patients were discharged. The mean time interval between onset of symptoms and hospital admission was 3.6 days (minimum 2 days, maximum 7 days, standard deviation 1.2 days). Twenty-one patients (23.3%) were admitted in the hemorrhagic phase, and 69 patients (76.7%) were admitted during the pre-hemorrhagic phase of infection.

A total of 132 relatives were enrolled in the study: 3 relatives for 7 patients, 2 relatives for 28 patients, and 1 relative for 55 patients. Seventy-four of these relatives were male (56.1%) and 58 were female (43.9%) with a median age of 40.5 years (17–69). Among the initial blood samples for 132 relatives,

*Address correspondence to Mustafa Gokhan Gozel, Department of Infectious Diseases and Clinical Microbiology, Cumhuriyet University Medical School, 58140, Sivas, Turkey. E-mail: mggozel@yahoo.com

TABLE 1
Characteristics of Crimean-Congo hemorrhagic fever (CCHF) positive patients' relatives diagnosed as seropositive and seronegative

Characteristics (n)	CCHFV IgG (-) n (%)	CCHFV IgG (+) n (%)	P
Gender			
Female (58)	56 (96.2)	2 (3.8)	0.07
Male (74)	60 (81.1)	14 (18.9)	
Age groups (years)			
17-40 (66)	63 (95.5)	3 (4.5)	0.026
41-60 (53)	43 (81.1)	10 (18.9)	
> 60 (13)	10 (76.9)	3 (23.1)	
Occupation			
Housewife (26)	26 (100)	0 (0)	0.002
Farmer (24)	22 (91.7)	2 (8.3)	
Animal husbandry (38)	27 (71.1)	11 (28.9)	
Other* (44)	41 (93.2)	3 (6.8)	
Living in CCHF-endemic area			
No (12)	12 (100)	0 (0)	-
Yes (120)	104 (86.7)	16 (13.3)	
History of close contact with a confirmed CCHF case			
No	116 (87.9)	16 (12.1)	-
Yes	0 (0)	0 (0)	

*Other occupations including teacher, student, worker, police officer, taxi driver, and shopkeeper.

16 (12.1%) were positive for CCHFV-IgG, but all were CCHFV-IgM negative. Two (3.8%) of 58 female relatives and 14 (18.9%) of 74 male relatives were seropositive for CCHFV-IgG ($P = 0.07$). The mean ages of seropositive and seronegative relatives were 47.5 years and 40.7 years, respectively ($P = 0.039$). Those relatives that reported animal husbandry as an occupation had higher rates of IgG seropositivity (28.9%, $P = 0.002$) (Table 1).

Sixteen seropositive relatives were excluded, because they had protective immunity; therefore, a total of 116 relatives were included in the study. Most of the kin were first-degree relatives, and most of relatives did not have a high risk, but

TABLE 2
The degree of kinship of close relatives diagnosed as seronegative for Crimean-Congo hemorrhagic fever virus (CCHFV) and the type of contact with confirmed CCHF cases

Characteristics	n (%)
Degree of kinship with patient	
Son or daughter	44 (37.9)
Mother or father	15 (12.9)
Wife or husband	29 (25.0)
Brother or sister	16 (13.8)
Other*	12 (10.4)
Type of contact with confirmed CCHF cases (either home and/or hospital care)	
Injured skin and blood or sanguineous body fluids†	0 (0)
Mucosa and blood or sanguineous body fluids†	0 (0)
Intact skin and blood	2 (1.7)
Intact skin and sanguineous body fluid†	0 (0)
Sexual intercourse	0 (0)
Physical contact with a CCHF patient without wearing gloves (excluding contact with bodily fluids)	81 (69.8)
Less than 1 m to proximity to a CCHF patient (without masks)	116 (100)
Use of the same toilet	79 (68.1)
Living in the same household with a CCHF patient	77 (66.4)
Stay as caregiver in a CCHF patient room for at least 24 hours	92 (79.3)

*Other degree of kinship including cousin, uncle, aunt, or close friend.

†Sanguineous body fluids including saliva, sweat, vomitus, feces, and urine.

a low risk contact (Table 2). None of the close relatives developed any signs or symptoms compatible with CCHF, all their second blood samples were negative for CCHFV-IgM and IgG.

The aim of the study was not to determine the seroprevalence of CCHF. However, the close relatives were more representative of a high-risk group than the general population, and we found the total seropositivity for CCHFV-IgG to be 12.1%. This result was similar to other seroprevalence studies reported in high-risk populations in Turkey.^{15,16} None of the seropositive relatives had a history of CCHF or similar clinical profiles, which led us to conclude that they may have experienced previous subclinical infections. Gender (male, $P = 0.07$), age (> 60 years, $P = 0.026$) and the occupation of animal husbandry ($P = 0.002$) were associated with IgG positivity. As highlighted in previous studies, being an older male could be a predisposing factor for exposure as a result of increased time spent in the field.^{7,15,16}

Nosocomial CCHF outbreaks with considerable mortality among health care workers have been well described.^{10,17-21} We did not identify any high-risk patterns of contact such as percutaneous exposure or mucous membrane contact. Contacts with intact skin of CCHF positive patients and blood were reported in only two subjects, but seroconversion was not observed at either instance.

The potential for CCHFV transmission through sexual contact has not yet been described.^{12,22} Although 29 relatives (25.0%) of our study group were spouses of CCHF-positive patients, they had no sexual contact with their patient during the acute phase of infection. Confirmation of sexual contact as a route for CCHFV transmission requires further study.

Although airborne transmission of CCHFV has not been documented in humans, transmission of the Ebola hemorrhagic fever virus by this route has been reported in animals.^{12,23-25} Gurbuz and others⁴ reported a case of nosocomial transmission, but emphasized that the infection source of the secondary case is not known for certain. They noted that contact with the index case's blood or body fluid was possible, with a remote possibility of airborne transmission. In this study, relatives nursed their patients without protective equipment, spouses shared the same bed, and family members had lived in the same household even using the same toilet until the patients' clinical status had deteriorated enough to require hospitalization. If the patients required support for walking, they were assisted and sometimes embraced by their relatives before they were transferred to hospital. Therefore, various types of contact, including direct physical contact with patients and objects around the patient without gloves, and respiratory contact such as droplet contact and airborne had occurred many times before hospital admission. All of the close relative subjects included in our study reported proximity of < 1 m from the patient, and 81 (69.8%) of them reported touching the patient without gloves. Despite all these physical and respiratory contacts, none of the patients' relatives developed any signs and symptoms of CCHF infection. The CCHFV IgM and IgG were negative in all second blood samples and the possibility of subclinical infection was excluded.

This study had some limitations. Although we aimed to include all relatives who had potentially risky contact with the patients, we had to exclude the relatives who did not return to the hospital for follow-up or who refused to give a second blood sample. However, we could determine that they

had not developed any clinical signs of infection by a phone interview. Second, it was repeatedly emphasized that although protective measures must be followed when handling patients and their wastes, many relatives did not comply with these measures, presumably because of strong emotional ties.

In conclusion, we found no serological evidence of CCHFV transmission in traced contacts among relatives who were involved in CCHF patients care at home and in the hospital. The promising results from this study indicate that CCHFV is not easily transmitted from person to person by physical or respiratory contacts as long as basic precautions and avoidance of high-risk activities such as percutaneous and mucosal contact are observed.

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Authors' addresses: Mustafa Gokhan Gozel, Mehmet Bakir, Aynur Engin, Ilyas Dokmetas, and Nazif Elaldi, Department of Infectious Diseases and Clinical Microbiology, Cumhuriyet University Medical School, Sivas, Turkey, E mails: mggozel@yahoo.com, mehmetbakir57@yahoo.com.tr, aynurum2000@yahoo.com, idokmetas@yahoo.com.tr, and nelaldi61@yahoo.com. Atifet Yasemin Oztup, Department of Medical Microbiology, Cumhuriyet University Medical School, Sivas, Turkey, E-mail: yaseminoztop@yahoo.com.tr

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