

CRIMEAN-CONGO HEMORRHAGIC FEVER AMONG HEALTH CARE WORKERS IN IRAN: A SEROPREVALENCE STUDY IN TWO ENDEMIC REGIONS

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Abstract. Crimean-Congo hemorrhagic fever (CCHF) has repeatedly caused nosocomial outbreaks among hospital staff. In the summer of 2003, we studied the seroprevalence of anti-CCHF IgG among health care workers who had come in contact with Crimean-Congo hemorrhagic fever patients from three referral hospitals in endemic regions of Iran. A total of 223 eligible staff were examined. Whereas 5 of 129 (3.87%) exposed health care workers tested positive, none of the 94 in the unexposed group did ($P = 0.075$). Seropositivity was more frequent among those whose intact skin had come in contact with nonsanguineous body fluids (9.52%) and those who had had percutaneous contacts (7.14%). Health care workers exposed to Crimean-Congo hemorrhagic fever patients, those who live in Sistan-Baluchestan province, and older health care workers were more prone to seropositivity. Where introduction of high-risk modes of contact cannot be confined, we propose that health care workers take all the protective measures when handling Crimean-Congo hemorrhagic fever patients, particularly their blood and other body fluids.

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal viral infection found in parts of Africa, Asia, Eastern Europe, and the Middle East.^{1,2} Nosocomial outbreaks of the disease with high mortality among hospital staff are frequent.^{3–8} In 1999, a nosocomial outbreak of CCHF was reported from Iran (Mardani M, unpublished data). In some rare serologic studies among health care workers (HCWs), the prevalence of anti-CCHF antibody was 0–1%.^{5,9,10}

To find out the extent, if any, to which contact with CCHF patients can cause hospital staff to test positive for anti-CCHF antibody, we studied the seroprevalence among those HCWs who had come in contact with CCHF patients in three referral hospitals in Sistan-Baluchestan and Isfahan, the two provinces of Iran with the highest confirmed cases of CCHF in the 2001 outbreak.¹¹

MATERIALS AND METHODS

A historical cohort study was conducted in the summer of 2003 in three referral university hospitals in Sistan-Baluchestan (in south-eastern Iran) and Isfahan (in central Iran) provinces. These referral hospitals are responsible for reporting suspected CCHF cases from the two provinces to the Pasteur Institute of Iran, the national center.¹¹ All hospital staff working in the admissions wards or laboratories who had a history of contact with CCHF patients or their blood or body fluids since 2001 were deemed eligible to register for the study as the exposed group; staff of other wards of these hospitals where CCHF patients had not been admitted according to the hospital records and who had no history of contact with any CCHF patients formed the unexposed group. Those with a history of contact with animal blood or carcasses or of tick bites were excluded from both the groups.

After short (30-minute) briefing sessions, 77.90% (268/344) of the workers, 81.07% (167/206) from wards deemed exposed and 87.68% (121/138) from unexposed wards, completed the screening questionnaire that also asked the staff to indicate their willingness to participate in the study.

A pre-tested self-administered questionnaire was used for data collection. The participants completed the questionnaire anonymously, and confidentiality was maintained. The questionnaire asked for information on age, sex, residential area, job, and educational level. The exposed staff described their routes of contact with CCHF patients by selecting one or more of the five proposed routes of exposure: (1) contact between injured skin and blood or other body fluids (the percutaneous route); (2) direct contact (without gloves) between intact skin and blood; (3) direct contact between intact skin and nonsanguineous body fluids; (4) direct skin-to-skin contact; and (5) exposure or respiratory contact, defined as closeness to CCHF patient(s) without any actual contact while not wearing a mask. The co-workers of the study helped the respondents in completing the questionnaire by explaining and answering questions as required.

Blood samples (10 mL each) were collected from the enrolled subjects, immediately centrifuged in the local laboratory, and transmitted in ice bags within 6 hours to the arbovirus and hemorrhagic fevers' laboratory of the Pasteur Institute of Iran, the reference laboratory in Tehran. Sera were checked by ELISA method for CCHF virus-specific IgG antibodies.¹² Samples that revealed positive results were rechecked and were also tested for the virus-specific IgM to exclude acute infection.

Data were analyzed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL) and Stata Statistical Software, version 8.0 (StataCorp LP, Geneva, Switzerland). For each point prevalence, 95% confidence intervals (CI) were calculated. Fisher's exact and χ^2 (for qualitative variables) as well as Wilcoxon-Mann-Whitney (for quantitative variables) tests were used to compare the characteristics of the study groups. For multivariate analysis, logistic regression was performed with enter method including study group, residential province, sex, age, educational level, and job variables. Confidence intervals for odds ratios, Wald test statistic (testing the null hypothesis that

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TABLE 1

Numbers and proportions of anti-CCHF IgG-positive staff in the exposed group

Characteristics	IgG+/n	IgG+,%	95% CI
All	5/129	3.87	0.55–7.20
Age*			
≤ 29 years	0/52	0	–
30–39 years	1/36	2.78	–2.66–8.22
≥ 40 years	4/32	12.50	0.86–24.14
Unknown	0/9	0	–
Gender			
Female	3/66	4.54	–.51–9.61
%	51.16		
Male	2/63	3.17	–1.19–7.53
%	48.84		
Province			
Systan-Baluchestan	5/67	7.46	1.12–13.80
%	51.94		
Isfahan	0/62	0	–
%	48.06		
Job			
Physician	0/23	0	–
%	17.83		
Non-physicians	5/106	4.72	0.66–8.77
%	82.17		
Route of contact to CCHF patients			
Percutaneous	1/14	7.14	–6.89–20.99
%	10.85		
Intact skin to blood	2/51	3.92	–1.48–9.28
%	39.53		
Intact skin to body fluids	2/21	9.52	–3.35–22.40
%	16.28		
Skin-to-skin	0/31	0	–
%	24.03		
Respiratory	2/64	3.13	–1.19–7.39
%	49.61		

CI = confidence interval.

* $P = .018$ for Wilcoxon-Mann-Whitney test, significant older age of IgG + compared to IgG – group (42.80 ± 9.68 vs. 32.39 ± 7.66).

the relative risk of seropositivity associated with the predictor variable is unity) and associated P values with one degree of freedom were calculated. The goodness-of-fit of the model was shown by the 2 log likelihood (–2LL), the Nagelkerke R^2 , and was tested by Hosmer-Lemeshow test. Statistical significance was set at $P < 0.05$.

RESULTS

Based on the responses to the questionnaire, 151 staff from the exposed group were considered eligible, 129 of which (85.43%) agreed to participate; in the unexposed group, 102 were considered eligible, 94 of which (92.16%) agreed to participate, taking the total number of participants (n) to 223. The mean age was 33.35 ± 7.97 years (range 19–57 years) and 115 were females (51.57%). There were no significant differ-

ences between the exposed and the unexposed groups in terms of general characteristics.

In the exposed group, 5 of 129 (3.87%, 95% CI: 0.55–7.20, Table 1) tested positive for anti-CCHF IgG; in the unexposed group, none tested positive (Fisher's exact test $P = 0.075$). All IgG-positive cases were from Systan-Baluchestan province and all were IgM negative (Table 2). In univariate analysis, age was the only variable that showed a significant difference between the IgG positive and negative subgroups within the exposed group (Table 1). Similarly, only the older subjects showed significant relation with seropositivity in multivariate analysis (odds ratio = 1.32; 95% CI: 1.03–1.69). Despite insignificant Wald test P value, the regression coefficients for both study group (3E + 8) and residential province (2E + 8) were found to be very large. The 2 log likelihood (–2LL) of 23.30, Nagelkerke R^2 of 0.54, and insignificant Hosmer-Lemeshow test ($\chi^2 = 0.91$, $P = 0.99$) indicated that the model used for multivariate analysis did fit the data.

In the exposed group, 59 (45.74%) cited more than one route of contact with CCHF patients. Although none of the five contact modes was significantly related to seropositivity, intact skin to body fluids (9.52%) and percutaneous contacts (7.14%) showed the closest relation whereas skin-to-skin contact had the least relation with no seropositivity (Table 1).

DISCUSSION

In current study, 3.87% of HCWs in the exposed group and none in the unexposed group tested positive for anti-CCHF IgG. Although a P value of 0.075 for this difference is below the assumed significance level, probably due to the limited number of seropositive cases ($N = 5$), a high regression coefficient for association between being a member of the exposed group and seropositivity, despite the insignificant Wald test P value, suggests contact with CCHF patients as a risk factor. Indeed, in this model the regression coefficients of two variables, namely residential province and study group were very large and therefore, we cannot rely on the Wald statistics for hypothesis testing.¹³ With a significant albeit weak odds ratio of 1.32, being older proved to be a risk factor for seropositivity, a finding supported by similar results (namely seroprevalence among the elderly) from other studies,^{5,14–16} which might be due to the chance of high-risk exposures increased by age.

The rate of IgG seropositivity found in this study was higher than that found in other rare reports of seroprevalence among staff with a history of contact with CCHF patients.^{5,9,10} This variation might be due to the differences in study powers, in the degree to which the staff observed the mandatory precautions, and in the amount of potentially harmful contacts.

TABLE 2
Characteristics of seropositive cases

Cases	Province	Sex	Age (year)	Job	Education	Contact type	IgM	Symptoms*
No. 1	Systan-Baluchestan	Female	40	Nurse aid	High school diploma	Percutaneous†	–	None
No. 2	Systan-Baluchestan	Female	44	Orderly	Secondary school	Intact skin to body fluids except blood‡	–	None
No. 3	Systan-Baluchestan	Male	43	Lab personnel	High school diploma	Intact skin to blood	–	None
No. 4	Systan-Baluchestan	Male	57	Orderly	Secondary school	Respiratory	–	None
No. 5	Systan-Baluchestan	Female	30	Nurse	Bachelor of Science	Intact skin to blood	–	None

* Hemorrhagic fever symptoms (i.e.) bleeding from multiple sites, fever, and myalgia.

† Case No. 1 also reported intact skin contact to body fluids.

‡ Case No. 2 also reported respiratory contact.

The limited number of seropositive cases compared with seronegative ones in exposed group (5 versus 124) precludes any statistical correlation between seropositivity and any of the five routes of potentially harmful contact. Although percutaneous exposure is believed to impose the highest risk of transmission,^{6,7,17} evidence regarding other routes is controversial. Although airborne transmission has not been documented in humans,^{5,17,18} some reports of infection with other viral hemorrhagic fever viruses like Ebola virus in animals through this route^{19,20} as well as infection without any documented direct exposure to infectious material²¹ make it impossible to rule out the risk from any mode of exposure. Our finding one seropositive orderly who had a history only of respiratory contact, despite the recall bias, also supports this conclusion and suggests that HCWs should observe all safety measures including barrier nursing and isolation as well as using face shields or surgical masks, eye protection, and gloves as appropriate when handling infected patients, their blood and other body fluids, or even when simply working in proximity to CCHF patients.

Our study has a few serious limitations. Firstly, recall could bias the recruitment of exposed and unexposed groups although hospital records were also used to determine the history of contacts. Furthermore, we limited the history of exposure to CCHF patients to 2 years before the study as one of our inclusion criterion. Secondly, although each type of exposure was fully defined and described both in the questionnaire and during the briefing sessions, the same recall bias together with failure to recognize the contact route, especially by inadequately qualified staff, could affect the validity of the history of prior contact. Thirdly, the rarity of seropositive cases, over which the authors had no control, together with the relative multitude of the routes for hospital staff to come in contact with patients made it difficult to assess the risk associated with each specific route.

In conclusion, we found that HCWs in contact with CCHF patients, those who live in Sistan-Baluchestan province, and those who are older are more likely to test positive for anti-CCHF IgG. All the HCWs, and particularly those in the three high-risk categories mentioned earlier, should take all protective measures whenever they are likely to come in contact with CCHF patients or with their blood and other body fluids unless further studies exclude any of the possible routes of contact.

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