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The seroprevalance of Crimean-Congo haemorrhagic fever in people living in the same environment with Crimean-Congo haemorrhagic fever patients in an endemic region in Turkey

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SUMMARY

Crimean-Congo haemorrhagic fever (CCHF) is endemic in Turkey, and since 2004 many cases have been reported from different regions of Turkey. There are limited data about the seroprevalence of the disease in household members of patients or persons sharing the same environment. We evaluated seroprevalence of CCHF in the immediate neighbourhood and in household members of patients living in the same environment as confirmed cases of CCHF in an endemic area of Turkey. A total of 625 healthy subjects [mean (S.D.) age: 42·3 (18·4) years, 58·7% females] without a past history of CCHF infection included in this case-control, retrospective study were evaluated in terms of sociodemographic characteristics, risk factors for CCHF via a study questionnaire, while serum analysis for CCHF virus (CCHFV) IgG antibodies was performed by ELISA. Anti-CCHFV IgG antibodies were positive in 85 (13·6%) participants. None of the seropositive individuals had a history of symptomatic infection. Regression analysis revealed that animal husbandry [odds ratio (OR) 1·84, 95% confidence interval (CI) 1·09–3·11], contact with animals (OR 2·31, 95% CI 1·08–5·10), contact with ticks (OR 3·45, 95% CI 1·87–6·46), removing ticks from animals by hand (OR 2·48, 95% CI 1·48–4·18) and living in a rural area (OR 4·05, 95% CI 1·65–10·56) were associated with increased odds of having IgG seropositivity, while being a household member of a patient with prior CCHF infection had no influence on seropositivity rates. This result also supports the idea that CCHF is not transmitted person-to-person by the airborne route.

Key words: Anti-CCHFV IgG antibodies, Bunyaviridae, Crimean-Congo haemorrhagic fever, viral haemorrhagic fever, zoonotic diseases.

INTRODUCTION

Crimean-Congo haemorrhagic fever (CCHF) is a fatal tick-borne zoonotic disease caused by *Nairovirus* of the Bunyaviridae family [1]. Known as a severe disease in humans with a high mortality rate (2·8–70%) [2, 3], the CCHF virus is transmitted to humans either by the bite of *Hyalomma marginatum* ticks or by direct contact with blood or tissues from infected humans or viraemic livestock [1–3]. CCHF has been reported from different parts of Africa, Eastern Europe, the Balkans, the Middle East and Central and Southern Asia [4, 5]. The first cases of CCHF infection in Turkey were recognized in the Kelkit Valley region in 2002. Since then, the number of cases in Turkey has increased to the magnitude of an outbreak including Central, Northern and Eastern Anatolia

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Fig. 1 [*colour online*]. Provinces included in the study from the Black Sea Region of Turkey endemic for Crimean-Congo haemorrhagic fever.

and Eastern Black Sea regions [6–8]. CCHF cases from countries that border Turkey, including Bulgaria, Greece, Iran and Iraq, have also been reported [5, 9–11]. While the clinical spectrum of CCHF infection may range from asymptomatic infection to severe haemorrhagic disease, most studies to date have included only symptomatic cases, leading to a paucity of data concerning the real incidence of infection, the full spectrum of severity of disease and its epidemiological features [12]. There are limited data about the seroprevalence of the disease in household members of patients or persons sharing the same environment where infected ticks are abundant. This study was therefore designed to determine the seroprevalence of CCHF infection and risk factors for disease in people living in the same environment with confirmed patients, either as household members or in the immediate neighbourhood, in the endemic area in the Black Sea region of Turkey.

METHODS

This case-control, retrospective study was designed and performed by the Karadeniz Technical University Medical Faculty Department of Infectious Diseases and Clinical Microbiology in endemic areas of Turkey, including Gumushane, Giresun, Artvin and Erzincan provinces in the Black Sea region in 2009–2010 (Fig. 1). The records of patients with serologically and clinically confirmed CCHF monitored between 2004 and 2008 were re-examined retrospectively. Patients' settlement areas and addresses were recorded. The study team visited patients' homes or their local environment and applied the study questionnaire via face-to-face interview. They collected blood samples from at least four persons living as household members or in the close neighbourhood of each patient. The questionnaire form included items on socio-demographic characteristics (age, gender, location of residence, occupation) and items related to risk factors for CCHF infection (animal husbandry, involvement in animal slaughter, contact with animals, contact with ticks, tick bite, removing ticks by hand, symptoms of CCHF, being a household member of a CCHF-positive patient).

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Karadeniz Technical University Medical Faculty Ethics Committe.

Serum samples obtained via centrifugation of collected whole-blood samples were kept at −80 °C until analysis for specific IgG antibodies against the CCHF virus (CCHFV) using a commercial ELISA kit (Vector-Best, Russia) according to the manufacturer's instructions. Although the sensitivity and specificity of the CCHV IgG ELISA were not specified by the manufacturer, studies that used this method have reported a sensitivity of 87–98·3% and a specificity of 99–100% [12]. The assay was performed at the Virology Reference Laboratory of the Refik Saydam Hygiene Institute of the Turkish Ministry of Health.

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Table 1. *Baseline characteristics of the study population and risk factors for IgG seropositivity (n=625)*

		Anti-CCHFV IgG				
	Total ($n=625$)	Positive ($n=85$)	Negative ($n=540$)	*P* value*	OR	95% CI
Age, years						
Mean (S.D.)	42·3 (18·4)	47·6 (16·3)	41·5 (18·6)	0·005†		
Gender						
Female/male	367/258	52/33	315/225	0·621	1·13	0·69–1·85
Characteristic, *n* (%)						
Farming	461 (73·8)	68 (80·0)	393 (72·8)	0·146	1·59	0·87–2·95
Animal husbandry	366 (58·6)	60 (70·6)	306 (56·7)	**0·021**	1·84	**1·09–3·11**
Involvement in animal slaughter	145 (23·2)	22 (25·9)	123 (22·8)	0·635	1·18	0·67–2·05
Contact with animals	500 (80·0)	76 (89·4)	424 (78·5)	**0·029**	2·31	**1·08–5·10**
Contact with ticks	380 (60·5)	70 (82·4)	310 (57·4)	**0·00002**	3·45	**1·87–6·46**
Tick bite	121 (19·4)	18 (21·2)	103 (19·1)	0·770	1·13	0·62–2·06
Removing ticks from animals by hand	317 (50·7)	59 (69·4)	258 (47·8)	**0·0003**	2·48	**1·48–4·18**
Being a household member of patient	272 (43·5)	34 (40·0)	238 (44·1)	0·481	0·85	0·52–1·38
Living in a rural area	491 (78·6)	79 (92·9)	412 (76·3)	**0·001**	4·05	**1·65–10·56**

OR, Odds ratio; CI, confidence interval.
* *P* value of Yates' corrected χ^2 test for CCHFV IgG serology subgroup comparison.
† Student's *t* test.

Statistical analysis

Statistical analysis was performed using SPSS version 13·0 (SPSS Inc., USA). Descriptive statistics (mean, standard deviation, count and percentage) were used to summarize the results. Nominal variables were compared using the χ^2 test with Yates' correction, and continuous variables were compared using Student's *t* test. The probabilities of relevant factors were calculated, and the results are given as odds ratios and 95% confidence intervals. Data are expressed as mean (standard deviation; S.D.), percent (%), median (min–max) and odds ratio (OR); 95% confidence interval (CI; min–max) where appropriate. $P<0·05$ was considered statistically significant.

RESULTS

A total of 625 healthy individuals living as household members or in the immediate neighbourhood of 145 confirmed CCHF cases (participant:patient ratio 4:3) in the same endemic area of Turkey were enrolled. The female:male ratio was 1·4:1 (58·7/41·3%) and the mean (S.D.) age of overall population was 42·3 (18·4) years.

Anti-CCHFV IgG antibodies were determined in 13·6% of individuals living as household members or in the immediate neighbourhood of confirmed CCHF patients ($n=85$). Seropositive individuals were significantly older than seronegative individuals [mean (S.D.) 47·6 (16·3) and 41·5 (18·6) years, respectively, $P=0·005$]. None of the anti-CCHFV IgG-positive individuals had a history of symptomatic infection for CCHF. Most of the study population were from rural areas (78·6%) and involved in farming (73·8), while 58·6% were involved in animal husbandry. Contact with animals was identified in 80·0% of subjects, contact with ticks in 60·5%, tick bite in 19·4% and removing ticks from animals by hand in 50·7% of the study population. A total of 272 (43·5%) individuals were household members of CCHF patients (Table 1).

Animal husbandry (70·6% *vs.* 56·7%, $P=0·021$), contact with animals (89·4% *vs.* 78·5%, $P=0·029$), contact with ticks (82·4% *vs.* 57·4%, $P=0·00002$), removing ticks from animals by hand (69·4% *vs.* 47·8%, $P=0·0003$) and living in a rural area (92·9% *vs.* 76·3%, $P=0·001$) were determined in a significantly higher percentage of anti-CCHFV IgG-positive individuals compared to IgG negative individuals, respectively. Farming, involvement in animal slaughter, past history of tick bite and being a household member of a confirmed CCHF patient had no significant effect on IgG seropositivity ($P=0·481$). Univariate analysis revealed that animal husbandry (OR 1·84, 95% CI 1·09–3·11), contact with animals (OR 2·31,

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95% CI 1·08–5·10), contact with ticks (OR 3·45, 95% CI 1·87–6·46), removing ticks from animals by hand (OR, 2·48, 95% CI, 1·48–4·18) and living in a rural area (OR 4·05, 95% CI 1·65–10·56) were associated with an increased probability of anti-CCHFV IgG seropositivity (Table 1).

DISCUSSION

Our findings, related to CCHF seroprevalence in people living in close proximity to patients in CCHF-endemic areas, revealed an overall anti- CCHF IgG positivity of 13·6% in healthy individuals. These were mostly from rural areas (78·6%) and involved in farming (73·8%) and animal husbandry (58·6%). Living in a rural area, involvement in animal husbandry, contact with animals, contact with ticks and removal of ticks from animals by hand were significantly associated with higher ratios and increased probabilities of anti-CCHF IgG positivity, while being a household member of a CCHF-positive patient had no significant influence on seropositivity rates.

Reported seroprevalences range from 0·024% in Iran [13] to 24·3% in Kosovo [14] in endemic areas, and as high as 30·3% of individuals involved in animal husbandry in Oman [15]. Expected CCHFV seroprevalence in high-risk persons has been reported at 10% during epidemics [16] or as low as 0·5% in non-epidemic situations [17]. Accordingly, seroprevalence studies from Turkey have shown variable seropositivity rates. In a study by Serter in 1980 [18], one of the initial seroprevalence studies in Turkey, a rate of 9·2% was determined using the haemagglutination inhibition method. In 2003, CCHFV seroprevalence in 40 veterinarians in the Tokat region was 2·5% [19], while no seropositivity was detected in healthcare workers [20]. Ergonul *et al.* [19] conducted a study in veterinarians from two separate regions of Turkey: Tokat (cited as an endemic province in the study) and Aydin (cited as a non-endemic province) in 2006 and reported a seropositivity rate of 3% in veterinarians from Tokat, but no seropositivity in veterinarians from Aydin. In a small survey in Turkey by Gunes *et al.* [21], a higher rate of IgG seropositivity was reported in rural areas than in urban ones (12·8% *vs.* 2%) in endemic provinces (Sivas and Tokat). In a previous seroepidemiological survey by Bodur *et al.* [12], seroprevalence of infection was reported at 10% in a sample from an outbreak region with 88% of infections estimated to be subclinical. In a recent study by Ertugrul *et al.*, seroprevalence was reported at 19·6% in inhabitants living in the endemic regions of Western Anatolia [22].

Underlying the higher risk for CCHFV infection in people who work in farming and animal husbandry, vector ticks are generally present on cattle in Turkey [22]. Accordingly, in line with the indication of higher CCHFV seroprevalence in persons living in rural areas than in urban areas of the CCHFV epicentre in Turkey in a study by Gunes *et al.* (12·8% *vs.* 2·0%) [21], our study also showed that living in a rural area was significantly more common in seropositive compared to seronegative subjects (92·9% *vs.* 76·3%, $P = 0{\cdot}001$) and was associated with increased probability of IgG seropositivity (OR 4·05, 95% CI 1·65–10·56).

The higher seroprevalence rates seen in individuals from rural areas and involved in animal husbandry in our study population seem to be in accordance with the much higher seroprevalence rate (19·6%) of the disease reported in a previous study by Ertugrul *et al.* in a study population consisting mainly of rural dwellers, with 39% of the participants being involved in animal husbandry [22].

Overall tick-bite frequency of 62% has been reported in persons at high risk and in 40–60% of CCHF patients in Turkey [21, 23]. Ertugrul *et al.* [22] reported that the most significant characteristic of seropositive subjects was exposure to tick bite (41·1%), despite a relatively low rate of tick-bite history (21·0%). In our study population, while contact with ticks (89·4%) was one of the most significant characteristics of seropositive individuals, a history of tick bite was present in only 19·4% of the overall population with similar seropositivity rates in individuals with (21·2%) or without (19·1%) a history of tick bite. Therefore, as reported previously [22], the high rate of CCHF seropositivity in individuals engaged in animal husbandry despite the low rate of tick-bite history appears to be associated with failure to recognize tick bites. Accordingly, a history of tick bite and tick removal from animals have been reported to be significantly associated with CCHF seropositivity in endemic areas including Tokat and Sivas provinces in Turkey [21]. Removing ticks from animals by hand, but not a history of tick bite, was reported to be associated with increased probability of IgG seropositivity in our study population.

In agreement with previous reports indicating that animal husbandry and farming were significantly associated with CCHF seropositivity due to the

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presence of vector ticks on the ground and on animals, the most significant characteristics of seropositive subjects were living in a rural area (92·9%), contact with animals (89·4%) and contact with ticks (82·4%). In this regard, given the likelihood of failure to recognize tick bites in most of our study population, it should be noted that personal protective measures such as regular examination of clothing and skin for ticks, appropriate tick removal, and use of repellents have been cited as crucial in order to prevent CCHF infection [3].

Risk factors associated with increased probability of seropositivity in the present study are in agreement with risk factors shown to be predictive of seropositivity in symptomatic patients in our previous studies [6, 7, 24]. Additionally, seropositive individuals were significantly older than seronegative subjects in our study. This supports the results of previous studies in Turkey indicating that the distribution of seropositivity increases with age [12, 22], particularly in those aged >40 years, due to increased opportunities for contact with vector ticks and presence of infection in the region long before it was recognized [21–26].

In a previous study by Gunes *et al.* [21], 11·4% of individuals were documented with a history of close contact with a CCHF-infected patient. While seropositivity in these individuals was 15·7%, this transmission route for CCHF was not reported to be statistically significant. Similarly, Ertugrul *et al.* [22] reported that presence of relatives infected with the virus was not significantly associated with CCHFV seropositivity. Therefore, being a household member of a patient was not associated with increased seropositivity, with similar percentages of household members being determined in the seropositive (40·0%) and seronegative (44·1%) groups in our study. This suggests that person-to-person airborne transmission of CCHF infection is unlikely, with no risk for individuals living close to CCHF-infected patients, sharing the same home or routine daily activities. This finding is compatible with other studies concerning viral haemorrhagic fever and indicating lack of person-to-person airborne transmission [27].

The clinical spectrum of CCHF includes mild, moderate, and severe forms [3, 28]. No asymptomatic form has yet been identified,. However, based on there being a higher rate of IgG positivity than the rate at which the disease is seen, particularly in endemic regions, asymptomatic infection has been reported to play a role the clinical spectrum of the disease [12]. In this regard, given that none of the seropositive individuals had CCHF symptoms, our finding of a CCHF prevalence of 13·6% seems to support the likelihood of a subclinical form of the disease. Similarly, previous studies concerning seroprevalence of CCHF in Turkey have reported infection seroprevalence of 10% in volunteers ($n = 3557$) from rural residential areas of Turkey, with a subclinical form of the disease in almost 90% of cases [12] and an infection seroprevalence of 19·6% in volunteers ($n = 429$) from a province in Turkey. A total of 39 cases were reported in that region between 2006 and 2010 [22]. In fact, the subclinical form of the disease was estimated in almost 90% of cases suggesting that the spectrum of severity was highly skewed towards milder disease in those years [12]. Nevertheless, the likelihood of misdiagnosed cases should not be disregarded, since the non-specific clinical course associated with the mild form of the disease manifests itself with headache, fever, sore throat, and sometimes nausea, vomiting, and diarrhoea, which may lead to misdiagnosis and CCHF patients being followed up with inaccurate diagnoses [22].

Data for subclinical cases have been considered epidemiologically important for estimating the level of herd immunity in the population and predicting the characteristics of outbreaks [12]. Hence, given the likelihood of an asymptomatic form of the disease as well as a mild form manifesting itself with non-specific symptoms in asymptomatic but seropositive individuals (13·6%) in our study, consideration of CCHF in the differential diagnosis of patients presenting with non-specific symptoms, particularly in endemic areas, seems crucial to the accurate diagnosis of mild forms of the disease in clinical practice. Additionally, while factors such as immune response of the host, viral load, or lack of some receptors were reported to be likely to affect the clinical form of the infection [29, 30], the exact reasons underlying individual differences in the clinical course of the disease are as yet unknown [31, 32]. Therefore, timely detection and comparison of different clinical groups will be helpful in clarification of the pathogenicity of the virus or host responses and in developing effective therapeutic management [12].

In conclusion, our findings indicate the likelihood of an asymptomatic or subclinical course in CCHF infection in individuals living in close proximity to patients in areas endemic for CCHF. As with symptomatic patients, living in a rural area, being involved in animal husbandry, contact with animals, contact with ticks and removing ticks from animals by hand

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were associated with an increased probability of anti-CCHF IgG positivity, with no risk of person-to-person airborne transmission. Given the likelihood of misdiagnosed cases and the epidemiological importance of confirmation of the subclinical form of the disease, consideration of CCHF in the differential diagnosis of patients presenting with non-specific symptoms in the clinical setting, particularly in endemic areas, seems crucial. Large-scale prospective studies in different clinical groups are now needed.

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DECLARATION OF INTEREST

None.

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