A SURVEY of CRIMINAL-CONGO HEAMORRHAGIC FEVER VIRUS in the RURAL PROVINCE of KONYA

KONYA İLİ KIRSALINDA KIRIM KONGO KANAMALI ATEŞİ VİRUSUNUN ARAŞTIRILMASI

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ABSTRACT

Aim: *Crimean-Congo haemorrhagic fever (CCHF) is one of the major viral infections that may be spread by ticks to humans. Animals can get the CCHV virus (CCHFV) without showing any symptoms of disease. Detection of CCHFV in animals can be used as a sign for the circulation of virus in the field. Therefore, the purpose of this study was to determine the prevalence of CCHFV in sheep and goats.*

Material and Methods: *In this study, prevalence of CCHF was investigated using blood and sera (n = 267) samples from 161 sheep and 106 goats from epidemiologically independent flocks (n = 29) in the Konya Province.*

Results: *The seropositivity in small ruminants was 21.3% (95% CI 16.4 - 26.2). CCHFV specific antibodies were detected in 30 sheep (18.6%, 95% CI: 12.6 - 24.7) whereas 27 out of the 106 goats (25.5%, 95% CI: 17.2 - 33.8) was found positive. CCHFV seropositivity was not statistically different between species (p = 0.222) and sexes (p = 0.455). CCHFV RNA was not detected. Seropositivity of CCHFV was higher in animals older than 2 years old (p = 0.009).*

Conclusion: *The current study's results suggest that CCHFV circulates in small ruminants in study area and people are at risk of getting CCHFV infection. Future epidemiological studies are required to determine foci of CCHFV in Türkiye.*

Key words: Crimean-Congo haemorrhagic fever virus, prevalence, small ruminants, risk factors

ÖZET

Amaç: *Kırım Kongo Kanamalı Ateşi (KKKA), keneler yoluyla insanlara bulaşabilen önemli viral enfeksiyonlardan birisidir. Hayvanlar, herhangi bir hastalık belirtisi göstermeden KKKA virusunu (KKKAV) alabilirler. Hayvanlarda KKKAV'nin saptanması, sahada KKKAV'nin sirkülasyonunun bir işareti olarak kullanılabilir. Bu nedenle, bu çalışmanın amacı koyun ve keçilerde KKKAV prevalansını belirlemekti.*

Gereç ve Yöntem: *Bu çalışmada, Konya İl'indeki epidemiyolojik olarak bağımsız sürülerden (n = 29),161 koyun ve 106 keçiden alınan kan ve serum (n = 267) örnekleri kullanılarak KKKA prevalansı araştırıldı*

Bulgular: *Küçükbaş hayvanlarda seropozitifliğin %21,3 (%95 CI 16,4 - 26,2) olduğu belirlendi. KKKAV spesifik antikorlar 30 koyunda (%18,6, %95 CI: 12,6 - 24,7) saptanırken, 106 keçinin 27'si (%25,5, %95 CI: 17,2 - 33,8) pozitif bulundu. KKKAV seropozitifliği türler (p = 0,222) ve cinsiyetler (p = 0,455) arasında istatistiksel olarak farklı değildi. KKKAV RNA'sı tespit edilmedi. KKKAV seropozitifliği 2 yaşından büyük hayvanlarda daha yüksekti (p = 0,009).*

Sonuçlar: *Mevcut çalışmanın sonuçları, KKKAV'nin çalışma alanındaki küçükbaş hayvanlarda sirküle olduğunu ve insanların KKKAV enfeksiyonuna yakalanma riski altında olduğunu göstermektedir. Türkiye'de KKKAV odaklarını belirlemek için gelecekteki epidemiyolojik çalışmalara ihtiyaç vardır.*

Anahtar sözcükler: Kırım Kongo kanamalı ateşi virüsü, prevalans, küçük ruminant, risk faktörleri

INTRODUCTION

Crimean-Congo haemorrhagic fever (CCHF) is a viral zoonotic disease that can cause fatal haemorrhagic disease in humans. The disease in humans is characterised by fever, flu-like symptoms, thrombocytopenia, haemorrhage and multi organ failure, and case fatality rates range from 5 to 73% (Schwarz et al., 1997; Ergönül, 2006; Papa, 2010). There is an increased risk for specific occupations (such as healthcare workers, veterinarians, farmers and butchers) since exposure risk to be bitten by infected ticks or close contact with tissues and blood of viraemic livestock and patients (Whitehouse, 2004). Although there are studies to develop a vaccine against CCHF, none of them have been approved.

The Crimean-Congo haemorrhagic fever orthonairovirus (CCHFV), renamed as orthonairovirus haemorrhagiae, has been detected in 35 tick species. However, Hyalomma ticks, especially Hyalomma marginatum, are the major vector of CCHFV (Hoogstraal, 1979). In addition, Rhipicephalus bursa contributes to the spread of CCHFV (Gargili et al., 2017). Because transovarial and transstadial transmission are possible in ticks, ticks are also reservoir of the CCHFV (Gargili et al., 2017).

CCHFV is classified within the Orthonairovirus genus in the Nairoviridae family. The virus has segmented, single-stranded and (-) sense RNA genome which include three segments; S (small), M (medium) and L (large) segments (ICTV, 2021). Higher genetic diversity has been observed in CCHFV than other tick-borne viruses, which reveals rich genetic variations of the virus (Mild et al., 2010). According to the molecular characterization of the S segment, nine genetically distinct clades of CCHFV have so far been identified: genotypes I, II, IIIa, and IIIb in Africa; genotypes IVa, and IVb in Asia; and genotypes V, VI, and VII in Europe (Gruber et al., 2019).

Although clinical forms of the disease are shown in humans, CCHFV can also infect livestock, birds, ticks and wild mammals (Portillo et al., 2021). Domestic and wild ungulates have roles in amplification of the virus and spread of the disease, but they do not show clinical signs of the disease (Estrada-Peña et al., 2013).

According to several studies human CCHF cases have been found throughout Europe, the Middle East, Asia, and Africa (Mohamed et al., 2008; Chinikar et al., 2010; Portillo et al., 2021; Shahhosseini et al., 2021). Seroepidemiological and molecular studies have been used to detect CCHFV foci in the field (Spengler et al., 2016). The presence of antibodies in the serum can provide evidence of their exposure to the virus, and detection of CCHFV antibodies in the domestic and wild animals can be used as a sign for the circulation of CCHFV in the field (Schuster et al., 2016). The serological and molecular detection of CCHFV infection have been reported in Türkiye (Ergönül, 2006; Tuncer et al., 2014; Özdemir et al., 2016). CCHFV infection is endemic in the middle Black Sea region of Türkiye (Albayrak et al., 2012; Leblebicioglu et al., 2016). Nowadays, human CCHF cases have been detected in non-endemic regions of Türkiye such as Marmara region and Central Anatolia (Tuncer et al., 2014; Özdemir et al., 2016). Although virus detection and tick survey studies have been carried out in these regions, epidemiological studies of CCHF in small ruminants are scant. Therefore, aim of the study was to assess the prevalence of CCHF in sheep and goats.

MATERIALS and METHODS

Study area

The current study was carried out in the Konya province in the Middle Anatolian region of Türkiye during January 2016 and August 2017. Konya province has an average elevation of 1031 m and latitudes of 37°52′ N and 32°29′ E (Wikipedia, 2023). Sheep and goats rearing are one of the important economic sources of income in rural areas of Konya Province. It has continental climate. The annual average temperature of the Konya Province was 11.9°C with annual average rainfall of 325 mm (Turkish State Meteorological Service, 2023).

Sample collection

The sample size was calculated based on 95% confidence interval with a precision of 6% and expected prevalence of 50% using Epi Info software (Ceylan & Günay , 2022; Kaplan et al., 2022b). EDTA whole blood and sera samples were taken from goats (n = 106) and sheep (n = 161) from epidemiologically distinct flocks (n = 29) in the Konya Province (Table 1). Seven to eight animals were randomly selected in each selected flocks. The sampled animals showed no signs of clinical illness. The vacutainer tubes which had anticlotting agent were used for molecular analyses. The information about the species, age and sex of the animal were written each sample tubes. Sera samples were used for detection CCHFV antibodies whereas EDTA whole blood samples were centrifuged for 10 min at 2200 rpm and obtained buffy coat cells were used for RNA extraction.

Serological analysis

The detection of sera IgG antibodies specific to CCHFV was performed using a commercial ELISA kit (Vectorbest, Koltsovo, Russia). Sera were inactivated at 56°C for 30 min to inactivate heat labile proteins before performing serological analysis. It has been reported that ELISA kit has 99% specificity and 98% sensitivity (Mertens et al., 2015). The serological analysis was performed according to kit's procedure using an ELISA reader (Epoch, BIO-TEK, USA). All sera samples were run in duplicate.

Viral RNA extraction

Viral RNA extracted from the buffy coat cells using a commercial extraction kit (QIAamp Viral RNA Mini Kit, Qiagen Germany), and extracted RNA were kept at -80°C until one step real-time RT-PCR analysis**.**

Quantitative one step real-time RT-PCR

Quantitative one step real-time RT-PCR was used in this study because it is more sensitive than conventional PCR and it allows seeing the results while the analysis is ongoing (Görkem et al., 2020). The probe and primers reported by Wölfel et al. (2007) were used in one step real-time RT-PCR analysis. Master mix was prepared with one step kit (RealTime ready RNA Virus Master, Roche, Germany) including 5 µl extracted RNA. Amplification reaction was performed

with using Light Cycler 2.0 PCR machine (Roche Applied Science, USA), with following conditions: 50 °C for 20 min, 95 °C for 5 min, and 45 cycles of 95 °C for 15 sec, 60 °C for 30 sec. Nuclease-free water was used as negative control.

Statistical analysis

Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, USA). The chi-square test and Fisher's exact test were used to determine the association between seropositivity and species, sex and age (Aygör & Düdükcü, 2019; Batı et al., 2021; Şen et al., 2022; Yapalı et al., 2022). A p-value of ≤ 0.05 was considered statistically significant. Bayesian approach of the beta distribution was used to determine CCHFV seroprevalence and 95% confidence intervals (Çunkuş et al., 2021; Kaplan et al., 2022a).

Ethics statement

This research was performed with the permission of General Directorate of Food and Control dated 07.02.2017 and numbered E.295166, and was carried out according to regulation on the Working Procedures and Principles of the Animal Experiments Ethics Committees published by the Ministry of Agriculture and Forestry (2014).

RESULTS

The CCHFV seropositivity in small ruminants was 21.3% (95% CI 16.4 - 26.2). Results of the serological analysis are presented in Table 1. CCHFV specific antibodies were detected in 30 sheep (18.6%, 95% CI: 12.6 - 24.7) whereas 27 out of the 106 goats (25.5%, 95% CI: 17.2 - 33.8) were found positive. No statistical difference in seroprevalence was observed between sheep and goats (p = 0.222). Furthermore, no CCHFV specific RNA was detected in tested buffy coat cells. Seropositivity of CCHFV was higher in animals older than 2 years old (p = 0.009). However, CCHFV seropositivity was not statistically different between species (p = 0.222) and sexes (p = 0.455). If a flock had one seropositive animal that flock was defined as infected flock. In the current study, 12 of the 29 flocks had at least one CCHFV seropositive animal.

Table 1. Seroprevalence of CCHFV in sheep and goats in the Konya Province.

Sex	Age group			
	0-24 months		> 24 months	
	No. examined	Positive, (%)	No. examined	Positive, (%)
Female	73	9 (12.3%)	79	26 (32.9%)
Male	38	6 (15.8%)	77	16 (20.8%)
Total	111	15 (13.5%)	156	42 (26.9%)

DISCUSSION

The first CCHF outbreak was reported in 2002 in Tokat Province in Türkiye. Later, CCHF cases have been reported in Black Sea region and the northern parts of the Central Anatolia of Türkiye (Leblebicioglu et al., 2016). CCHF has spread westwards of the Türkiye (Tuncer et al., 2014). It has been reported that domestic and wild ungulates serve as reservoirs for CCHFV, and they have significant role in the transmission of the virus (Camicas et al., 1990; Appannanavar & Mishra, 2011). Survey studies are important to better understand epidemiological status of the infection and to identify potential risk areas. However, there is no surveillance programme in Türkiye. Furthermore, there are limited studies on the status of the disease in sheep and goats in Türkiye. Therefore, in this study, prevalence of CCHFV in sheep and goats was investigated.

In this study, CCHFV seropositivity of sheep and goats in the study area was 21.3%. This finding was higher than that observed in a previous study from Türkiye that approximated seropositivity of 17.2% (Nurettin et al., 2022). However, CCHFV seropositivity in the current research was lower than previous field researches which were carried out in the Marmara and Black Sea regions of Türkiye. Albayrak et al. (2012) reported seropositivity of CCHFV in sheep and goats were 85.7% and 66.7%, respectively in the Black Sea region of Türkiye (Albayrak et al., 2012). Furthermore, Tuncer et al. (2014) reported seropositivity of CCHFV in sheep and goats were 31.8% and 66.0%, respectively in the Marmara region of Türkiye. The differences in seropositivity of CCHFV between current study and different studies might be related to the tick species located in the study area, the age of animals, the sampling strategy and management conditions.

There have been reports of varied CCHFV seropositivity from different countries. According to reports, seroprevalence of CCHFV in sheep were 16.2% in Azerbaijan (Spengler et al., 2016), 20.0% in Iraq (Al-Yabis et al., 2005), 25% in Greece (Papa et al., 2014), 27.8% in Romania (Ceianu et al., 2012), 41.9% in Iran (Telmadarraiy et al., 2010), 50.0% in India (Mourya et al., 2012) and 74.0% in Bulgaria (Barthel et al., 2014) whereas in goats were 10.0% in Kosovo (Fajs et al., 2014), 20.0% in Albania (Papa et al., 2009), 30.3% in India (Mourya et al., 2012), 46.0% in Iran (Chinikar et al., 2010) and 62.3% in Bulgaria (Spengler et al., 2016). The differences in seropositivity of CCHFV in different countries might be related to the age of the sampled animals, the number of sampled animals and flocks and difference in management

conditions. Also, seroprevalence rate can change depending on the tick species located in the study area which contribute to the transmission of the virus.

Similar to previous studies, CCHFV seropositivity was not found to be statistically significant depending on species (Schulz et al., 2021; Nurettin et al., 2022). In the current study, CCHFV seropositivity was higher in goats (25.5%) than in sheep (18.6%), but the difference was not significant. However, previous research which was carried out in Albania reported that prevalence rate was significantly higher in sheep than in goats (Schuster et al., 2016). Possible explanations for this result might be related to the age of the animals, the number of sampled animals and flocks and the individual differences.

In the present study, seropositivity of CCHFV was higher in animals older than 2 years old ($p = 0.009$). This result agrees with previous research that reported higher seropositivity in the older age categories (Mohamed et al., 2008; Schulz et al., 2021). Older animals have high frequency of pasture usage than young animals. Therefore, higher seropositivity in animals older than 2 years old can be explained by increased risk of being bitten by infected ticks on pasture.

In this study, CCHFV seropositivity was not statistically different between female and male animals ($p = 0.455$). Sargianou et al. (2013) have also been reported that sex has no influence on CCHFV seropositivity.

In the current study, CCHFV specific RNA was not detected in sampled animals. This result may be explained by the period of viraemic phase. Duration of viraemic phase in sheep and goats ranges between 7 and 15 days (Whitehouse, 2004). Therefore, presence of neutralising antibody in sampled animals may explain why CCHFV specific RNA could not detected.

CONCLUSION and SUGGESTIONS

The current study's results suggest that CCHFV circulates in small ruminants in study area and people are at risk of getting CCHFV infection. However, current study's results are not enough to determine the regional and country-based profile of the CCHFV infection in Türkiye. Future epidemiological researches are needed to determine CCHFV foci in Türkiye.

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Conflict of Interest
There is no conflict of interest.

KAYNAKLAR

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