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An outbreak of Crimean-Congo hemorrhagic fever in western Anatolia, Turkey

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Summary
Objective: Sporadic Crimean-Congo hemorrhagic fever (CCHF) cases were first reported in Turkey in 2002, arising particularly in northeastern Anatolia. Epidemics have been reported in neighboring countries since the 1970s. With the increase in number of CCHF virus infected or suspected cases in the Aydin region of western Anatolia by 2006, we decided to focus attention on this disease.
Methods: Twenty-six patients with an acute febrile syndrome characterized by malaise, bleeding, leukopenia, and thrombocytopenia were admitted to various hospitals in Aydin between May 2007 and June 2008. CCHF diagnosis was established by measuring IgM in a blood sample and/or detecting viral genome by real-time polymerase chain reaction (real-time PCR) or by clinical findings of the disease, even if IgM was negative (real-time PCR was not performed).
Results: Twenty-five patients (22 of the patients with cases confirmed by laboratory findings) matched the criteria for CCHF defined by the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD); one patient did not match suspected-case criteria, however he was also included in the study as his blood sample was positive according to real-time PCR. The most common signs and symptoms encountered were fever, myalgia, nausea, and vomiting. The overall case-fatality rate was 5.5% (one patient) in 2007. Patients showed hemorrhagic manifestations (35%), while complete blood counts revealed thrombocytopenia and leukopenia in 17 patients (65%), and raised levels of aspartate aminotransferase (77%), alanine aminotransferase (77%), lactate dehydrogenase (69%), and creatinine phosphokinase (42%).
Conclusions: To date, western Anatolia has been accepted as a non-endemic area for this disease, with only sporadic cases. These non-endemic CCHF cases in Aydin province of the

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Aegean region should alert other non-endemic regions of the world to be mindful of this disease.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a potentially fatal viral infection occurring in about 30 countries worldwide. It has the most extensive geographic range among the significant tick-borne viruses.[1,2] The virus belongs to the genus *Nairovirus* in the *Bunyaviridae* family and causes severe disease in humans, with a reported mortality rate of 5–80%.[3] The widespread geographic distribution of CCHF virus and its ability to produce severe human disease with high mortality rates make the virus an important human pathogen. Humans become infected through tick bites or direct contact with body fluids or tissues from viremic patients or viremic livestock.[1,2,4,5]

CCHF cases were first reported in Turkey in 2002, although epidemics have been reported from neighboring countries since the 1970 s.[1,2,4,6–9] Recently, a case report from Greece was published.[10] Between 2002 and 2007, a total of 1820 confirmed cases were reported to the Ministry of Health (MoH) of Turkey.[11] The diagnoses of these cases were performed through virus detection by PCR or IgM and/or IgG positivity on ELISA. All these patients were hospitalized, and the fatality rate was calculated as 5.3%. A great majority of the cases were seen in northeastern Anatolia (Tokat, Sivas, Gümüshane, Amasya, Yozgat and Corum provinces; Figure 1).[12] Western Anatolia and the Aegean region including Aydin is accepted as a non-endemic area (Figure 1).[13,14] By 2006, CCHF cases began to be recorded in Aydin. The cases reported in Aydin were all residents of the city and surroundings. Since Aydin is an important agricultural and tourism zone of Turkey showing an increase in CCHF cases, we decided to make a detailed analysis of this area.

Patients and methods

Patients

This was a retrospective descriptive study carried out between May 2007 and June 2008. A CCHF case report form, prepared by the MoH of Turkey, was filled out for all patients admitted for tick bites and/or suspicious cases as defined by the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD).[15] Admission date, age, gender, address, existing symptoms, epidemiological history, physical examination, and laboratory findings were recorded. Cases admitted for tick bites without any symptoms and normal laboratory findings were informed about CCHF and its consequences. They were advised to follow up their own body

Figure 1 Endemic provinces and Aydin on the map of Turkey.

temperatures and to attend the nearest hospital in the case of any symptoms related to the disease (i.e., fever over 38 °C, petechiae, hemorrhage without history of trauma). These cases were also reached by telephone call from the community health centers. Those with symptoms were hospitalized immediately in city hospitals. Similar forms were filled out for patients who were diagnosed with CCHF at other health centers in the city. Cases positive for CCHF virus IgM and/or positive real-time polymerase chain reaction (real-time PCR) or cases negative for IgM (real-time PCR not performed) but showing clinical findings of the disease (acute febrile syndrome characterized by malaise, bleeding, leukopenia, and thrombocytopenia) were included in the study. Cases whose blood samples were unavailable or cases who had no clinical and laboratory findings were excluded from the study.

Laboratory testing

Patient venous blood samples were stored in optimal conditions and sent to the Turkish MoH Refik Saydam National Hygiene Center for confirmation of the diagnosis.

TaqMan-based real-time PCR was performed as described by Yapar et al.[16] Five microliters of viral RNA were added to 20 μl of the mixture containing 5 pmol of each primer, 4 pmol of TaqMan probe, 0.2 mM of each dNTP (containing dUTP), and 6 mM $MgCl_2$. The cycle conditions were carried out as follows: a cycle of real time at 42 °C for 40 min, 95 °C for 10 min, followed by 40 PCR cycles of 15 s at 95 °C, 1 min at 60 °C . The assay was run on a Perkin—Elmer 7700 Sequence Detection System using the combination of reverse transcriptase (MBI Fermentas) and Hot Start Taq DNA polymerase (Bioron GmbH, Germany). The data were analyzed according to Yapar et al.[16]

CCHF IgM ELISA testing was performed at the Refik Saydam National Hygiene Center, Virology Research and Reference Laboratory following the recommendations of the Centers for Disease Control and Prevention (CDC, Atlanta, USA). CCHF IgM was detected by ELISA prepared with inactivated native CCHF viral antigens (Strain IbAr 10200) grown in Vero E6 cells on serum samples.[17]

Results

Venous blood samples were collected from 61 patients, 49 of them in 2007 and 12 in 2008. Among the samples taken, ELISA tests for specific CCHF IgM antibodies were positive for eight patients, and real-time PCR tests for CCHF were positive in 14. IgM was negative in four patients and real-time PCR was not performed on the blood samples of these cases; however, clinical findings in these patients (acute febrile syndrome characterized by malaise, bleeding, leukopenia, and thrombocytopenia) were concordant with CCHF. Thus, 26 patients were enrolled in the study. Twenty-five (96%) in 26 patients fulfilled the suspected-case criteria for CCHF of the ENIVD.[15] Only one patient did not match the suspected-case criteria, though he was also included in the study as real-time PCR analysis of his blood sample was positive, confirmed by repeat analyses. Of these 26 patients, 18 were admitted to various hospitals in Aydin between April and September 2007 and eight patients between May and June 2008. All cases were indigenous—autochthonous with no history of traveling to another CCHF endemic area (e.g., eastern Anatolia) in Turkey.

Table 1 Demographic and clinical characteristics of the patients

	Patients (%) (N = 26)
Males	15 (58)
Died	1 (5.5)[a]
History of tick bite	19 (73)
Living environment	
Urban	11 (42)
Rural	15 (58)
Symptoms and signs	
Fever	24 (92)
Headache	18 (69)
Myalgia	15 (58)
Abdominal pain	11 (42)
Nausea	18 (69)
Vomiting	12 (46)
Diarrhea	9 (35)
Hemorrhagic manifestations	9 (35)
Abnormal laboratory results	
AST—ALT elevation	20 (77)
LDH elevation	18 (69)
Leukopenia	17 (65)
Thrombocytopenia	17 (65)
CK elevation	11 (42)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine phosphokinase.
[a] The percentage is calculated based on 18 patients in 2007.

Fifteen patients were male and 11 were female. The mean ± SD age was 30.7 ± 20.6 years (range 2—69 years). Three (12%) of the patients were in the pediatric age group (0—15 years old). The most commonly encountered signs and symptoms were fever, headache, myalgia, nausea, and vomiting. Hemorrhagic manifestations were seen in nine (35%) patients. Demographic and clinical characteristics of the patients are shown in Table 1. The time period between the onset of symptoms and referral to hospital was 3 days on average (range 1—10 days). Eleven patients (42%) were admitted on the day the symptoms appeared. The mean ± SD hospitalization was 8.8 ± 4.2 days (range 2—17 days).

Seventeen (65%) of the 26 patients had received ribavirin therapy. The overall case-fatality rate was 5.5% (one patient) in 2007. The fatality was a 53-year-old woman who had had a tick extracted from her neck. She had presented to the hospital on the 10th day after symptoms had arisen. She had received therapy (ribavirin and conventional, i.e., blood transfusion, etc.), but died on the second day of hospitalization due to disseminated intravascular coagulopathy.

Thrombocytopenia and leukopenia were seen in 17 (65%) patients (Table 1). The results of laboratory tests performed at the time of admission to the hospital are shown in Table 2.

Table 2 Laboratory findings in patients at admission

	Patient mean (min–max)	SD
AST (U/L)	351.3 (17–3196)	667
ALT (U/L)	164.3 (13–931)	230.6
LDH (U/L)	684.1 (103–3301)	766.3
CK (U/L)	669.2 (8–4474)	1178.1
Platelet count ($\times 10^9$/l)	136.9695 (11.000–407.000)	102.3365
WBC count ($\times 10^9$/l)	4.8443 (0.800–17.900)	4.72279

SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine phosphokinase; WBC, white blood cell.

Discussion

There has been a substantial increase in reports of CCHF virus over the past 10 years. CCHF virus-infected cases were first reported in Turkey in 2002 and the number of cases has gradually increased.[3,18–20] The Turkish MoH handles the disease as an important public health problem, since for the last four years CCHF has been endemic in northeastern Anatolia. According to previous studies, northwestern Anatolia and the province of Aydin and its surroundings are accepted as non-endemic for CCHF.[3,13,18–24]

In 2006 blood samples were taken from cases mimicking CCHF infection in Aydin province; three of 14 blood samples serologically confirmed a diagnosis of CCHF. This could be taken as a signal of a potential widespread threat in our region. The Department of Infectious Diseases and Clinical Microbiology of Adnan Menderes University Medical Faculty together with the local health authorities have performed an informative study for the medical staff and the residents in this area. A public awareness campaign was launched, which included brochures, TV programs, and employee education programs on public health about early diagnosis and preventive measures concerning tick bites and CCHF infections.

Following this campaign, people began to present at health centers immediately following any tick bite. We determined that there was no admission for tick bite in 2006, but 1724 tick bite admissions were observed in 2007, with a further 1380 in the first half of 2008. Whether or not there was a history of existing tick bite, patients with complaints of the disease were admitted to health centers in 2007 and 2008, and were hospitalized in infectious diseases and clinical microbiology clinics of the state and university hospitals.

This is the first time that so many cases have been reported outside of the regions accepted as endemic. Does this mean that the disease in Turkey is spreading towards the west? It is hard to answer 'yes', since the disease has not been observed in the surrounding provinces, with the exception of sporadic cases. The ratio of agrarian in Aydin to the population of surrounding provinces is higher than in the surrounding provinces, and some geographical characteristics of this area are similar to those of endemic regions. The common geographical characteristic of regions where cases are diffusely observed is fragmental land with a combination of forestry and agricultural sections. Changes in climatic conditions have been suggested to be one of the factors that has facilitated reproduction of the tick population, and consequently the increased incidence of tick-borne infectious diseases.[1] The number of days with a temperature of over 5 °C in April, and the daily mean temperature in April in the region of Turkey affected by a recent outbreak were reported to be increased in the years before the outbreak.[25] The temperature levels in summer in Aydin resemble those of endemic regions where it is hot and arid. The mean temperature of Aydin in July is about 26.8 °C, while it is about 24.2 °C in eastern Anatolia.[26] The potential roles of migratory birds and the movement of livestock carrying ticks in the spread of the virus over distant geographic areas have been studied.[1] Birds migrating from the Balkans were suggested to be the cause of the 2002 outbreak in Turkey.[18] The Aydin region is on the migration route of migratory birds.

Both the climatic and geographic characteristics provide the appropriate environment for ticks to reproduce,[27] and these vectors spread to rural areas involved with agriculture via cattle, sheep, goats and small mammals such as hedgehogs, hares, and rodents. Residents in these areas work in fields in the summer, a time when the ticks are in their mature form and may be actively transferred to them by these animals. Following the campaign carried out in the Aydin region, admission to healthcare centers particularly increased in the summer months. As a consequence, the identification of infected patients has increased the recognition of this disease, and contrary to common belief it is concluded that the disease has been observed in our region, but could not have been recognized before.

This study is important for people visiting the region. Aydin is one of the important tourism centers in the Aegean region of western Anatolia, which had a population of about one million including the surrounding area in the year 2007. Every year, over one million tourists visit the region for its historic towns and sea tourism. To date, no CCHF cases have been reported from the popular tourist resorts in this area and the Aegean coast. The European Centre for Disease Prevention and Control advises travelers to affected areas to take general preventive measures to minimize exposure to tick bites, and people who have traveled to this area having symptoms after a tick bite are advised to contact their physician.[28] When suspected symptoms are observed in travelers on return to their home countries, CCHF should be considered in the differential diagnosis whether there is a history of tick bite or not. There are case reports and studies supporting this opinion.[29,30]

Although there is different information in the literature related to treatment with ribavirin, both the World Health Organization and the Turkish MoH recommend this treatment. Therefore, ribavirin was administered to 17 patients with CCHF at the time of admission in 2007. However, one of our cases was admitted to a health service for tick bite, but since clinical and laboratory findings were not concordant with CCHF, he was discharged home after the tick was extracted and advised to follow-up his body temperature. As his blood sample showed a positive result with real-time PCR (one day later), he was recalled. On second evaluation, he had no findings related with the disease and was considered as asymptomatic and did not receive ribavirin treatment. There is very little information showing that the disease may be asymptomatic.[31,32] Generally, there are three

different clinical presentations of CCHF — mild, moderate, and severe.[31,33] This case showed that there may be asymptomatic cases and this issue should be taken into consideration.

There are different ratios related with the mortality rate of the disease. The case-fatality rate has been estimated to range from 5% to 80% in various studies.[34,35] The mean mortality rate is between 20% and 50%. In studies performed in our country, mortality rates range between 5% and 20%.[3,18,19,33,36] This wide difference in mortality rates may be attributed to the infecting virus type (up to eight clades of CCHF virus have been observed worldwide) and patient care conditions.[1,18] The mortality rate in our cases was 5.5% in 2007, which correlates with other figures from Turkey. This low mortality rate might be due to the early admission of cases to hospitals and having supplementary treatment in the early stages of the disease.

The present study had several limitations. The first was its retrospective nature, which was dependent on the case report forms of the MoH. These forms did not include information on the severity of clinical presentation and therefore severity classification could not be performed. Since hemoglobin, prothrombin time, partial thromboplastin time, and bilirubin levels of all cases were not available, these values could not be included. Secondly, virus sequencing was not performed, so further studies are needed for genetic characterization of the strain. Another limitation was that there was no agreement between hospitals with regard to the protocols for ribavirin treatment, hence treatment criteria are not given.

Conclusions

This study emphasizes the widespread geographic distribution of CCHF virus, as it reports cases from a non-endemic region (Aydin). The similarity between natural environmental conditions and climatic properties of Aydin and endemic areas should be a warning to other non-endemic regions with the same characteristics. Therefore, disease-related campaigns should be carried out to help recognize potentially missed cases. Furthermore, as Aydin is one of the most popular tourism places in the world, entertaining over one million tourists every summer, this study should be a reference for the authorities in tourism.

Conflict of interest: No conflict of interest to declare.

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