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Crimean-Congo hemorrhagic fever in Greece: a public health perspective

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Summary In June 2008 the first non-imported fatal case of Crimean-Congo hemorrhagic fever (CCHF) was recorded in northern Greece. We present herein the public health interventions and the case definitions we developed for the epidemiological investigation. The possibility of CCHF establishing endemicity in this area is discussed.

The event

In June 2008 the Hellenic Center for Disease Control and Prevention (HCDCP; Athens, Greece) was notified about a case of Crimean-Congo hemorrhagic fever (CCHF) that had occurred in the Prefecture of Rhodopi, northern Greece. The case concerned a 46-year-old woman, who was engaged in agricultural activities and had a history of tick bite 1 day before the onset of symptoms. No travel abroad or contact with livestock, other animals, or an ill person was reported. The patient presented with fever in association with headache and nausea, however during the course of her disease she developed hematomas at injection sites, a diffuse petechial rash, and genital hemorrhage; she died 7 days following the onset of symptoms. The following results were found on laboratory investigation: white blood cell count, 5.62×10^9 cells/l (81.4% neutrophils and 15.5% lymphocytes); platelets, 100×10^9 cells/l; hemoglobin, 11.5 g/dl; hematocrit, 33.5%; glutamic oxaloacetic transaminase (SGOT), 3962 U/l; glutamic pyruvic transaminase (SGPT), 1545 U/l; lactate dehydrogenase, 8085 U/l. Coagulation parameters were: activated partial thromboplastin time (aPTT): 82.6 s; international normalized

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ratio (INR): 1.75; D-dimers: >10 000. The patient was tested for hantavirus, which causes hemorrhagic fever with renal syndrome (HFRS), leptospirosis, and rickettsial diseases; all results were negative. The diagnosis of CCHF was confirmed by reverse transcriptase-nested PCR and quantitative real time PCR at the World Health Organization (WHO) Collaborative Centre for Research and Reference on Arboviruses and Hemorrhagic Fever Viruses (Aristotle University of Thessaloniki, Greece). Sequencing analysis revealed that the causative strain was phylogenetically similar to the CCHF strains circulating in the Balkan countries north of Greece (Albania, Kosovo-Yugoslavia, Bulgaria), Turkey, and Southwest Russia.[1] Since then 15 additional, sporadic cases have tested negative for CCHF; all had a history of tick bite and fever. None of the contacts of the patient (family members or healthcare workers) developed any symptom. This is the first CCHF case in Greece.

Interventions

An ad hoc committee was established for the development of case definitions for CCHF notification and contact tracing (Table 1). Written guidelines for strict isolation and prompt management of CCHF cases within healthcare facilities were sent to hospitals in northern Greece (Table 2). Guidelines for appropriate disinfection of inanimate medical equipment, cleaning procedures, management of waste, handling and transportation of clinical specimens, management of accidental needle stick injuries and contact with blood or other potentially contaminated biological fluids, and management of dead bodies with suspect, probable, or confirmed CCHF were also sent to the hospitals. Information regarding prevention of tick bites and proper removal of attached ticks was disseminated to residents of and visitors to the Prefecture of Rhodopi. At the same time the event received considerable attention from the mass media leading to a surge in 'tick-phobia'. In response to this, the HCDCP informed the general population about CCHF, the associated risk for Greece, and preventive measures for tick bites.

In order to complete a risk assessment for CCHF in Greece, the following actions have been scheduled by the HCDCP and the ministries of health and agricultural development: (1) serosurveys in indigenous populations of all ages in northern Greece; (2) serosurveys in livestock animals throughout the northern border areas of Greece; and (3) testing ticks col-

Table 1 Case definitions for notification of Crimean-Congo hemorrhagic fever (July 2008)

Suspect case
A patient with abrupt onset of high fever >38.5 °C, and one of the following symptoms: severe headache, myalgias, nausea, vomiting, and/or diarrhea
AND
History of tick bite within 14 days prior to the onset of symptoms; or
History of contact with tissues, blood, or other biological fluids from a possibly infected animal (e.g., abattoir workers, livestock owners, veterinarians) within 14 days prior the onset of symptoms; or
Healthcare workers in healthcare facilities, with a history of exposure to a suspect, probable, or laboratory-confirmed CCHF case, within 14 days prior to the onset of symptoms
AND
The contact/exposure took place in the Prefecture of Rhodopi
Probable case
A probable CCHF case is defined as a suspected CCHF case fulfilling in addition the following criteria:
Thrombocytopenia
AND
Two of the following hemorrhagic manifestations: hematoma at an injection site, petechiae, purpuric rash, rhinorrhagia, hematemesis, hemoptysis, gastrointestinal hemorrhage, gingival hemorrhage, or any other hemorrhagic manifestation in the absence of any known precipitating factor for hemorrhagic manifestation
Confirmed case
A confirmed CCHF case is defined as a case that fulfills the criteria for probable CCHF and in addition is laboratory-confirmed at the World Health Organization (WHO) Collaborating Centre for Reference and Research on Arboviruses and Hemorrhagic Fever Viruses (Aristotle University of Thessaloniki, Thessaloniki, Greece) with one of the following assays:
Detection by ELISA or IFA of specific IgM antibodies against CCHF virus or a 4-fold increase in specific IgG antibodies against CCHF virus in two specimens collected in the acute and convalescence phases
Detection by RT-PCR of CCHF virus genome in a clinical specimen confirmed by sequencing of the PCR product
CCHF virus isolation
Contact tracing
History of contact with tissue, blood, or other biological fluids from the same possibly infected animal
Members of the patient's family
Healthcare workers with a history of exposure to a suspect, probable, or laboratory-confirmed CCHF case
The abovementioned categories should be followed for the onset of symptoms or fever (measurement of temperature every day) for a total of 14 days following the last contact.

ELISA, enzyme-linked immunosorbent assay; IFA, indirect immunofluorescence assay; RT-PCR, reverse transcriptase polymerase chain reaction.

Table 2 Guidelines for the prevention of transmission of CCHF within a healthcare facility and the prompt management of CCHF cases

Immediately isolate all suspect, probable, or confirmed CCHF cases under strict contact precautions
Use of personal protective equipment by all HCWs entering the isolation room
Notify all suspect, probable, or confirmed CCHF cases to the HCDCP
Inform the hospital Committee for Nosocomial Infections about the suspect, probable, or confirmed CCHF case
Educate HCWs about appropriate infection control measures
Send clinical specimens for laboratory diagnosis to the WHO Collaborating Centre for Reference and Research on Arboviruses and Hemorrhagic Fever Viruses (Aristotle University of Thessaloniki, Greece)
Consider administering ribavirin (in accordance with WHO recommendations). Ribavirin should be introduced within 3—4 days from the onset of symptoms and while awaiting laboratory results

CCHF, Crimean-Congo hemorrhagic fever; HCWs, healthcare workers; HCDCP: Hellenic Center for Disease Control and Prevention.

lected from domestic animals from northern Greece. Collection and testing of serum specimens from healthcare workers with a history of contact with the case is underway.

Discussion

CCHF is an acute, highly contagious, tick-borne viral zoonosis. Hemorrhagic manifestations develop in late-stage disease, and published mortality rates range from 10% to 50%. Of all tick-borne viruses, CCHF virus has the greatest geographic distribution, being endemic in more than 30 countries in Africa, central and southwestern Asia, the Middle East, and Eastern Europe.[2] Numerous domestic and wild animals may serve as hosts, including cattle, sheep, goats, horses, pigs, hares, ostriches, camels, donkeys, hedgehogs, mice, and domestic dogs.[2] Infection is transmitted to humans through the bite of ticks (mainly of the genus *Hyalomma*) or through unprotected contact with blood or tissues from infected animals or humans.[2—5] Nosocomial transmission is a major mode of acquisition of infection.[2] CCHF fulfills the criteria for immediate notification because of its high mortality, the potential for human-to-human transmission, the need for strict implementation of infection control measures, the availability of treatment with ribavirin, the potential of misdiagnosis of imported cases, and the potential use as a bioterrorism agent.[2] Hemorrhagic fevers are included in the list of diseases, along with pneumonic plague and yellow fever, for which the Revised International Health Regulations call for implementation of the decision algorithm to determine whether notification to the WHO is indicated.[6]

Over the last decade, climate, environmental, and anthropogenic factors have driven the expansion of CCHF endemic foci and the onset of community outbreaks. Such outbreaks were recorded in Kosovo in 2001 and Turkey in 2003—2008, countries neighboring Greece.[2,3,7,8] In April 2008, a cluster of probable CCHF cases occurred in southern Bulgaria, a few kilometers from the border with Greece.[9] Turkey and Balkan countries with the exception of Greece have recorded circulation of CCHF strains among animal hosts, ticks, and humans, and have established CCHF endemicity.[5] The wide outbreaks that occurred in Turkey were preceded by several decades of serologic evidence of a zoonotic CCHF focus.[2]

Available data indicate limited, if any, circulation of CCHF virus in Greece. In 1976 an asymptomatic, laboratory-acquired CCHF infection occurred in a veterinarian in Greece who was working with the AP-92 strain. The AP-92 CCHF virus strain was isolated from *Rhipicephalus bursa* ticks collected from goats in northern Greece, and differs from all other CCHF virus strains.[2,10] In a study conducted during 1980—1981 among 65 adults from villages in northern Greece, evidence of previous CCHF infection was found in four (6%), however none of them recalled any serious illness resembling CCHF.[11] Antoniadis et al. tested 3388 apparently healthy farmers, woodcutters, and shepherds from all over Greece from 1981 to 1988, of whom 1% had antibodies against CCHF virus.[12] Given the paucity of clinical CCHF cases in Greece during the last three decades, it appears that this seroprevalence reflects previous possible infection with the AP-92 strain and not with the pathogenic Balkan CCHF strain. Starting from 1982, Greek patients with a disease compatible with hemorrhagic fever have been tested and found negative for CCHF.

The establishment and maintenance of a CCHF endemic focus requires an environment favoring an efficient contact between competent ticks and animal hosts with relatively high prevalence of infection. Heterogeneity in infection levels may occur even within endemic foci, as a result of variable climate and environmental suitability for ticks and animal hosts.[3] To date, domestic animal serological data from northern Greece indicate no previous exposure to CCHF and thus it is highly unlikely that these animals could potentially serve as hosts (Greek Ministry of Agricultural Development, personal communication). This information needs to be further confirmed in future studies. However, recent studies reveal that Hyalomma ticks are abundant in northern Greece,[13,14] a finding that could be partially attributed to the increased (by approximately 2 °C) mean temperatures and mean maximum temperatures in this area during the last 25 years (Greek National Metereologic Services; personal communication). Pavlidou et al. found that of a total of 3249 ticks collected from domestic animals near oak and coniferous forests in 11 prefectures of northern Greece during 2003—2006, *Hyalomma marginatum* ticks accounted for 12.4% of all ticks, third to *Ixodes ricinus* and *R. bursa* ticks (44.57% and 19.15%, respectively).[14] In this study, *H. marginatum* ticks were found in all investigated prefectures. One could not exclude the possibility of CCHF becoming endemic in that area under conditions favoring suitable infection levels among animal hosts. Nevertheless, it appears that the current CCHF case was an isolated event, and transmission was achieved through a tick bite. CCHF should be considered in a patient with a history of tick bite and a compatible clinical syndrome in areas neighboring those with

established endemicity. In the Balkans, CCHF should be considered along with hantavirus HFRS, rickettsial infections, and leptospirosis — infections with similar clinical manifestations.

Case definitions constitute the basis for epidemiological surveillance and their performance may influence not only the accurate estimation of the spread of a disease, but also could compromise prompt responses and interventions at the patient, community, and hospital level. The development of case definitions for CCHF was a challenge for us, given the lack of experience on non-imported CCHF cases in other developed countries. Their application is not intended for diagnostic or therapeutic decisions, but targets the early and accurate detection of a CCHF case and its contacts, in order to trigger response measures for disease containment. The threshold of thrombocytopenia (150×10^9 platelets/l)[15] and the extension of the geographic area under epidemiological surveillance were thoroughly discussed. We aimed at the development of case definitions of suspect cases that had a good balance between an increased sensitivity (trying to catch early cases rapidly) and a lower specificity. This was important in order to react to the crisis and at the same time avoid overuse of resources, in a country with no circulation of CCHF virus to date. For this reason, an expansion of the area under surveillance to include a total of six prefectures in the regions of Thrace and Eastern Macedonia, instead of limiting surveillance to the Prefecture of Rhodopi where the first CCHF case occurred, was discussed. This discussion was based on the abundance of Hyalomma ticks in these areas in northern Greece.[14] In order to ensure the efficacy of our approach, case definitions should be tested in real practice and in a large number of cases, which was not the case here. Our case definitions have been forwarded to the European Center for Disease Control and will be considered for the development of uniform case definitions for non-imported CCHF cases within the European Union.

Over recent decades, alterations in natural ecosystems, intensive agriculture, global warming, and the exponential increase of movement of people for any cause have provided the framework for the expansion of several vector-borne diseases globally, from endemic areas to neighboring non-endemic areas as well as to distant continents.[7,16–20] The spread of West Nile virus from Africa to the east coast of the USA, followed by the expansion of this infection across this country within less than a decade, constitutes the most striking paradigm.[16] Global warming may also have influenced CCHF prevalence in already endemic areas by altering the ticks' growth pattern, but also in areas currently free of CCHF, by redirecting the migration routes of birds that host the affected ticks to areas newly warmed by the earth's altered temperature patterns.[7] Whether this will be the case for CCHF in Greece or for other vector-borne diseases in Europe and other developed countries with temperate climates in coming years is unknown. In the meantime, the public health sector, especially in Greece, which is at the crossroads between Africa, Europe, and Asia, has to be prepared for the worst-case scenario.

Conflict of interest: No conflict of interest to declare.

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