Article
https://doi.org/10.61900/SPJVS.2023.04.02

CRIMEAN-CONGO HEMORRHAGIC FEVER: A FUTURE HEALTH ISSUE IN FRANCE? WHAT ABOUT ROMANIA?

Serban MOROSAN[1,2*], Andreea COZMA[3], Anca DASCALU[3], Stephane MAROT[4]

Department of Public Health, Iasi University of Life Sciences, Romania[1]
Department of Exact Sciences, Iasi University of Life Sciences, Romania[3]
UMS28, Sorbonne Université/INSERM, Paris, France[2]
Pierre Louis Institute of Epidemiology and Public Health, Paris; and Pitié-Salpêtrière University Hospital, Paris[4]

[*]E-mail: serban.morosan@uaiasi.ro

Abstract

Crimean Congo Hemorrhagic Fever Virus (CCHFV) is the etiological agent of a severe hemorrhagic fever affecting Africa, Asia and southern Europe. In recent decades, climate change has led to an increase in the distribution range of this virus. Little scientific data is yet available on the interactions with its vector, the tick, or on its biology. However, the confirmed presence of human infections in Spain and positive serologies in Corsican livestock could well focus attention on this pathogen. This review takes stock of developments in eco-epidemiological knowledge of this virus, particularly in Europe and especially in France. What about Romania ?

Keywords: Crimean-Congo hemorragic fever, virus, emergent disease

Introduction

Crimean Congo Hemorrhagic Fever Virus (CCHFV) is the etiological agent of a severe hemorrhagic fever affecting Africa, Asia and southern Europe. In recent decades, climate change has led to an increase in the distribution range of this virus. As yet, little scientific data is available on interactions with its vector, the tick, or on its biology. However, the confirmed presence of human infections in Spain and positive serologies in Corsican livestock could well focus attention on this pathogen. This review takes stock of developments in eco-epiological knowledge of this virus, particularly in Europe and especially in France.

The viral cycle from an ecological standpoint

The distribution of the CCHFV virus overlaps with the location of various species of hard ticks in the Ixodidae family (notably the Hyalomma genus), its natural reservoirs. In the wild, *Hyalomma* tick larvae preferentially infect small mammals (rodents and lagomorphs) or birds, where they transform into nymphs. The nymphs then detach from their host and moult into adults, which seek out a new host, usually a large mammal. These large mammals thus serve as amplifying hosts without showing any symptoms. Infected female ticks lay eggs that carry the virus (transovarial transmission), giving rise to a new generation of infected vectors. Recently, reptiles have been added to the list of species playing a role in the circulation of CCHFV, with its discovery in the blood of Testudo turtles and in the *H. aegyptiacum* ticks that parasitize them. The disease is mainly transmitted to humans by tick bites, but it can also be transmitted through contact with biological fluids from infected animals, hence the high risk for livestock farmers, veterinarians, nursing staff and slaughterhouse personnel.

Most of the tick species that transmit the CCHFV virus belong to the hard tick family, the Ixodidae. These ticks are vectors of numerous viral and bacterial pathogens (causing tick-borne encephalitis, borreliosis, rickettsiosis, etc.). The CCHFV virus has been isolated mainly in Eurasia and Africa, from various ticks belonging mainly to the genus *Hyalomma*, but also from ticks of the genus *Amblyomma*, *Rhipicephalus* (and ssp boophilus*)*, *Ixodes*, *Haemaphysalis* or

Dermacentor. Ticks of the *Hyalomma* genus (as well as those of the Amblyomma genus) are known for their specific active hunting behaviour. These different Ixodes are characterized by feeding on one, two or three hosts during their lifetime. Ticks that feed on a single host during their development (e.g. Rhipicephalus of the Boophilus subgenus) represent only a small proportion of ticks associated with CCHFV. Ticks with two or three hosts, on the other hand, can transmit the virus to different branches of mammals. Unlike the Ixodidae family, ticks of the *Argasidae* family, known as soft ticks, are described as multi-host. They feed on 5 to 20 different hosts during the different stages of their life. Very few studies mention the presence of CCHFV in these species (only in the genera *Argas* and *Ornithodoros*), and attempts to infect these ticks with the virus in the laboratory have been unsuccessful. The short duration of the blood meal in these species seems to be associated with a lower capacity to transmit the virus, compared with Ixodidae, whose meal can last several days. In infected ticks, the virus is mainly found in the salivary glands and reproductive organs it is through saliva that the virus is transmitted. Several other viruses are currently under development, and should in future enable the virus to be transmitted to the parasitized animal.

Pathophysiology of infection

While infected animals are generally asymptomatic, humans can develop severe infection. The disease resulting from CCHFV infection has four phases: an incubation phase, a pre-haemorrhagic phase, a haemorrhagic phase and a convalescence phase, the duration and associated symptoms of which can vary considerably. The incubation period after a tick bite can last from one to three days, and in some cases more than a fortnight; this is linked to the mode of transmission of the disease (by the tick itself or by contaminated fluids). The pre-haemorrhagic phase is characterized by a sudden rise in fever, dizziness, headaches, photophobia and back and stomach pains. The hemorrhagic phase, which develops 3 to 6 days after the onset of the disease, is associated with petechiae1 and ecchymosis, blood in urine and feces, and external bleeding (nose, gums, skin, etc.). In the most severe cases, cerebral haemorrhage and massive liver necrosis can occur. These are associated with a poor prognosis.

In humans, hemorrhages are the consequence of endothelial cell fragility, due to infection, but also of a cascade of host-induced mechanisms in response to the virus. The resulting deregulation of hemostasis stems in particular from the induction of pro-inflammatory cytokine secretion and disseminated intravascular coagulation. The mortality rate of CCHF after natural infection varies between 5% and 40%. Nosocomial viral infections have also been observed. These have higher mortality rates, no doubt due to the greater viral inoculum involved. In this case, the virus is transmitted via contact between a contaminated patient's biological fluids and the caregiver's mucous membranes. This type of transmission has also been observed following veterinary care or in slaughterhouses.

Survivors undergo a long convalescence phase, starting 15 to 20 days after the onset of the disease. At present, only ribavirin is used to treat the infection. This nucleotide analogue appears to have some activity when used in the early stages of infection, although its efficacy remains debatable. Very recently, an American team demonstrated that the use of antibodies specific to GP38 (a soluble non-structural viral glycoprotein) could protect animals against the virus. GP38 is little studied, and this first discovery opens the way to new fields of research, both for understanding the virus and developing new treatments. A single vaccine is available, but only in Bulgaria.

Epidemiology du virus

In Tajikistan, texts dating back to the 12th century refer to a disease with haemorrhagic symptoms similar to those of CCHF. But it was in 1944, during the Second World War, in the Crimea, that the virus was first identified as the etiological agent of a contagious hemorrhagic fever that caused an epidemic. The virus responsible was isolated and named "Crimean haemorrhagic fever virus". In 1969, it turned out that this virus was in fact identical to the one responsible for Congo fever, which had been isolated.

Of Congo fever, isolated in 1956, hence the name "Crimean-Congo hemorrhagic fever virus" (CCHFV for the virus and CCHF for the disease). The CCHFV virus eventually proved endemic in over 30 countries across Africa, Asia, Europe and the Middle East.

This infection is a public health concern in view of its increasing range, particularly in Europe, and more specifically in Turkey and the Balkans. Currently, less than 20,000 cases of infection with this virus have been confirmed worldwide. In Turkey, no cases were identified before 2002; since then, over 9,700 cases have been diagnosed.
The geographical distribution of CCHFV coincides with that of ticks of the genus Hyalomma, notably H. marginatum, its main vector in Europe. These

ticks can be found sporadically as far north as Germany and Sweden, transported during avian migrations or livestock movements. The local climate in these regions did not allow these tick species to establish themselves permanently, but the recent discovery in Germany of ticks of the Hyalomma family that have completed their growth cycle suggests that these species could in future establish themselves at very high latitudes.

In France, several tick species with the potential to transmit CCHFV are present more or less locally: Ixodes ricinus, Dermacentor marginatus, Dermacentor reticulatus, Haemaphysalis punctata, as well as Rhipicephalus sanguineus and Hyalomma marginatum marginatum. Recent studies have shown the presence of breeding populations of H. marginatum, notably in the French Mediterranean region.

In France, the increase in the range of these ticks could be the result of avian migrations, but also, and to a significant extent, the transport of livestock (horses and cattle). This tick was already known in Corsica, where it has been established for many decades. Given the wide distribution of its vector, the many animal species that can serve as amplifying hosts, the favorable climate and climatic conditions in several European countries bordering the Mediterranean, there is a strong possibility that the range of the CCHFV virus will expand in the future. A model study of various climatic scenarios that could occur in the habitat areas of the various ticks has shown that an increase in temperature and a decrease in precipitation in the Mediterranean region will result in a sharp increase in their establishment in these suitable habitat areas, including their expansion northwards. In Eastern Europe, the first cases have been observed in Greece, and micro-epidemics (fewer than 20 cases) have been reported sporadically in the Balkans since 2001 (Croatia, Kosovo, Macedonia). In 2010, virus-carrying H. lusitanicum ticks were first collected from a deer in the Cáceres region of Spain, revealing the presence of the virus in Western Europe. More recently, virus-carrying ticks or serology-positive animals have been identified in several regions, including the Spanish region of Huesca, close to the French border. In September 2016, two cases of human infection, including one fatality, were reported in Avila ((province of Castile and Leon, 80 km from Madrid). A suspected case was also mentioned in 2018 in Badajoz in Extremadura (southwest of Spain), and a new case was detected in June 2020 in Salamanca. A seroprevalence study carried out among blood donors showed a seropositivity rate of around 1% in this region. In France, no cases have yet been reported, but the seropositivity rate seems high in Corsica, particularly among cattle (13%), sheep and goats (2 to 3%), even if no ticks carry the virus has not yet been detected and identified. The virus present in Spain was related to strains grouped in clade III (strains from southern and western Africa). Viruses belonging to this same clade have also been identified in Morocco, in birds, which suggests a possible introduction of the virus into Spain via migratory birds. Similarly, a tick carrying a virus of this clade III was collected from a meadow cat (Saxicola rubra), a species of passerine, on the island of Ventotene, off the coast of Naples in Italy, indicating a possible presence of the virus on the Italian island. territory. The viral strains present in Corsica have not yet been identified. Avian migration routes crossing Corsica being different from those crossing Spain, it is possible that the viral strains in these regions vector, and therefore of the virus are potentially divergent. A low pathogenic strain of the virus, strain AP92, initially isolated in Vergina in Greece, was also found in Turkey and in Algeria.

What about Romania

Recent studies have shown that this zoonosis is also circulating in animals in countries such as Romania and the former Yugoslav Republic of Macedonia (Nemeth V and al. 2013, Ceianu CS and al. 2012; Mertens M and al. 2015; Bratuleanu B. and al. 2022). In the last study in Southern Romania (2022), the overall seroprevalence of CCHF in small ruminants was 37.7% (95% CI 31.7 to 43.7). This high seroprevalence to CCHFV among ruminants indicates that CCHV or a closely related virus circulates in Southern Romania.

We performed a first human seroprevalence study for CCHFV with the Danube Delta National Institute for Research and Development and Sanitary Veterinary and Food Safety, Tulcea, Romania (article submitted). Our data showed that 38% of professional exposed workers (i.e. veterinarians and animal breeders) are seropositive for CCHFV antibodies. We also demonstrate a CCHFV seroprevalence of 26% in the control group (not professionally exposed). These data suggesting that the disease could be endemic, in the South-Est Romania region and argue to be confirmed in animals.

Conclusion

The presence of the virus in western Europe and in the Balkans, suggests that more and more cases are reported in Europe so in France as well. It is therefore important to continue to deepen our knowledge of this virus and to develop new antiviral molecules, vaccine strategies and diagnostic tests.

Bibliography

1. Connolly-Andersen A-M, Moll G, Andersson C, et al. Crimean-Congo hemorrhagic fever virus activates endothelial cells. J Virol 2011 ; 85 : 7766-74.
2. Xiao X, Feng Y, Zhu Z, et al. Identification of a putative Crimean-Congo hemorrhagic fever virus entry factor. Biochem Biophys Res Commun 2011 ; 411 : 253-8.
3. Hoogstraal H. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J Med Entomol 1979 ; 15 : 307-417
4. Estrada-Peña A, Venzal JM. Climate niches of tick species in the Mediterranean region: modeling of occurrence data, distributional constraints, and impact of climate change. J Med Entomol 2007 ; 44 : 1130-8.
5. Xia H, Beck AS, Gargili A, et al. Transstadial transmission and long-term association of crimean- congo hemorrhagic fever virus in ticks shapes genome plasticity. Sci Rep 2016 ; 6 : 1-12.
6. Kar S, Rodriguez SE, Akyildiz G, et al. Crimean-Congo hemorrhagic fever virus in tortoises and Hyalomma aegyptium ticks in East Thrace, Turkey: potential of a cryptic transmission cycle. Parasit Vectors 2020 ; 13 : 201.
7. Telmadarraiy Z, Chinikar S, Vatandoost H, et al. Vectors of Crimean Congo hemorrhagic fever virus in Iran. J Arthropod-Borne Dis 2015 ; 9 : 137-47.
8. Sureau P, Klein JM, Casals J, et al. Isolement des virus thogoto, wad medani, wanowrie et de la fièvre hémorragique de crimée-congo en Iran à partir de tiques d'animaux domestiques. Ann Inst Pasteur Virol 1980 ; 131 : 185-200.
9. Tahmasebi F, Ghiasi SM, Mostafavi E, et al. Molecular epidemiology of Crimean-Congo hemorrhagic fever virus genome isolated from ticks of Hamadan province of Iran. J Vector Borne Dis 2010 ; 47 : 211-6.
10. Shepherd AJ, Swanepoel R, Cornel AJ, et al. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 1989 ; 40 : 326-31.
11. Robert LL, Debboun M. 146 arthropods of public health importance. In : Ryan ET, Hill DR, Solomon T, et al., eds. Hunter's tropical medicine and emerging infectious diseases, 10th ed. London : Content Repository Only!, 2020 : 1055-62.
12. Dickson DL, Turell MJ. Replication and tissue tropisms of Crimean-Congo hemorrhagic fever virus in experimentally infected adult Hyalomma truncatum (Acari: Ixodidae). J Med Entomol 1992 ; 29 : 767-73.