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REVIEW ARTICLE

Ebola Haemorrhagic Fever – a Review

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Introduction

The Ebola virus was first identified during simultaneous outbreaks of haemorrhagic fever in the Democratic Republic of Congo[1] and Sudan.[2] Human Ebola infection probably occurs more frequently than was previously believed. Intensive surveillance for Ebola haemorrhagic fever in the equatorial region of the Democratic Republic of Congo between 1981 and 1985 suggested that Ebola haemorrhagic fever periodically emerges from nature to infect humans.[3] Since the increased awareness about Ebola, following the Kikwit 1995 outbreak,[4] two Ebola outbreaks have occurred in Gabon[5,6] and one nurse has died of Ebola haemorrhagic fever in South Africa after taking care of an infected Gabonese physician.[7] Prior to the Kikwit epidemic there had been two outbreaks with the Reston type of Ebola in imported monkeys in the U.S.A.[8,9] For these reasons there has been an increased scientific interest in Ebola haemorrhagic fever during recent years. In February 1999, the *Journal of Infectious Diseases* published a 288-page supplement on Ebola research.

In May 1999 haemorrhagic fever cases were reported from the north-east province of the Democratic Republic of Congo. A new Ebola outbreak was initially suspected, but later laboratory tests confirmed it was the first Marburg epidemic in Africa.[10]

A list of the known Ebola outbreaks is shown in Table I. In this review we will summarize what is currently known about Ebola haemorrhagic fever.

Virology

Ebola viruses, together with the Marburg virus, are the only members of the *Filoviridae*. By electron microscopy the Ebola and the Marburg viruses have a similar appearance.[11] There are four Ebola subtypes (Zaire, Sudan, Reston, Ivory Coast). The Reston type is not pathogenic for humans. The Ebola subtype found in the Democratic Republic of Congo, in Yambuku and Kikwit is genetically similar and is also similar to the Ebola virus, isolated from Gabon in 1994 and 1996.[12]

Clinical Manifestations

After an incubation period of 4–10 days, patients develop fever and may complain of headache. fatigue, arthralgia or myalgia, sore throat, dysphagia or odynophagia, anorexia, nausea, vomiting, abdominal pain, cough and diarrhoea.[13,14] A conjunctival infection is often an early clinical sign. A cutaneous rash may appear, but this may be difficult to identify in dark-skinned patients. The general condition rapidly deteriorates. Patients may develop hiccoughs, tachypnoea and bleeding (such as epistaxis, haematemesis, melena, petechiae, ecchymosis, bleeding at needle puncture sites, menorrhagia), oliguria and shock. Patients may also develop neurological symptoms such as convulsions, delirium and coma.

Patients generally die 6–9 weeks after the first symptoms[13,15], but differences in mortality have been observed between outbreaks and during an outbreak[15,16]. In surviving patients convalescence may be slow and is often characterized by fatigue and arthralgia. Uveitis[17] and orchitis, parotitis, hearing loss or tinnitus have been observed in a few patients.[18]

There is very little knowledge about the laboratory abnormalities that may occur during an Ebola haemorrhagic fever infection. Based on the few patients that have been studied and on non-human primate experiments, the following abnormalities have been observed: early lymphopenia with subsequent neutrophilia, and marked thrombocytopenia with an abnormal platelet aggregation.[19] Serum liver enzymes are elevated with normal or only moderately elevated alkaline phosphatase and bilirubin levels. [5,20]

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Table I. Ebola Haemorrhagic Fever: known cases and outbreaks.

Year	Ebola species	Country	Number of human cases	Percentage of deaths
1976	Ebola-Zaire	Zaire	318	88%
1976	Ebola-Sudan	Sudan	284	53%
1976	Ebola-Sudan	England	1	0%
1979	Ebola-Sudan	Sudan	34	65%
1989	Ebola-Reston	USA	0	0%
1990	Ebola-Reston	USA	0	0%
1992	Ebola-Reston	Italy	0	0%
1994	Ebola-Zaire	Gabon	44	63%
1994	Ebola-Ivory Coast	Ivory Coast	1	0%
1995	Ebola-Zaire	Zaire	315	81%
1996	Ebola-Zaire	Gabon	37	57%
1996	Ebola-Zaire	Gabon	60	75%
1996	Ebola-Zaire	South Africa	2	50%
1996	Ebola-Reston	USA	0	0%
1996	Ebola-Reston	Philippines	0	0%

Diagnosis

During an Ebola epidemic, Ebola haemorrhagic fever should be suspected, based on clinical manifestations and on a history of contact with a person with Ebola haemorrhagic fever. A problem, however, may be that patients may not reveal certain symptoms and may not mention a previous contact with an infected person, because Ebola haemorrhagic fever is a stigmatizing disease.[21,22] Therefore, suspected cases should be isolated and carefully observed to see whether characteristic clinical findings, such as haemorrhagic manifestations develop.[23] These manifestations, however, only develop in about 50% of cases.[13]

During recent epidemics, no laboratory tests have been available to confirm a diagnosis of Ebola haemorrhagic fever on site. Laboratory diagnoses were only made on stored samples, which were sent to specialized laboratories. Ebola viruses are relatively easy to isolate and propagate well in cell culture in high containment laboratories.[23] Acutely ill patients have a very high viraemia.[23] Direct detection of the Ebola virus can be done using immunofluorescent techniques, ELISA, immunohistochemistry and polymerase chain reaction (PCR).[23–25] Because large quantities of Ebola virus are present in dermal tissue, skin biopsies have been proposed for post-mortem confirmation of the Ebola infection for surveillance purposes.[25,26] Antibodies appear as patients recover. In the past, serological diagnosis of Ebola virus infection was made by indirect fluorescent antibody (IFA) test.[27] This test, however, has problems with specificity and sensitivity.[27] An IgM capture ELISA assay is more useful in the diagnosis of acute infections and a direct IgG ELISA test should replace the IFA for seroprevalence studies.[23,28,29]

Pathogenesis

Ebola viruses cause focal necrosis of liver, lymphoid organs, kidneys, testes and ovaries. Endothelial cells, macrophages, monocytes and hepatocytes are main targets of infection.[30] A marked elevation of interleukin-2, interleukin-10, tumour necrosis factor, interferon-alpha and gamma were noted in fatal Ebola haemorrhagic fever cases.[31]

Transmission

Ebola virus infection is transmitted through contact with blood or body fluids from infected patients or monkeys. The risk of transmission increases when there has been a contact with a patient in the later stages of illness.[32] In the first Ebola outbreak in the Democratic Republic of Congo, in Yambuku, the reuse of unsterilized needles and syringes was an important factor in the spread of the disease.[1] In the Kikwit outbreak, many hospital workers became infected because of inappropriate barrier precautions.[4,33] In the same way certain family members who were taking care of Ebola patients became infected. Others became infected during the ritual manipulation of corpses.[4,33] During the Kikwit epidemic no evidence was found of transmission of the Ebola virus from a convalescent patient to a household contact.[32] None of the 78 household members who had no physical contact with an Ebola case during the clinical illness became infected.[32] Because most patients who became infected had multiple contact with various body fluids, it is not clear to what degree these different fluids are able to transmit the infection.[32] It also remains unclear how the infection enters the body. The most likely route of infection is through

contact of contaminated fingers with the oral mucosa or conjunctiva. Aerosol transmission has been suggested among monkeys infected with the Reston and Zaire subtypes of Ebola virus.[9,34,35] Ebola virus has also been identified in alveoli of experimentally infected monkeys[36] and in human lung specimens, obtained during the Kikwit epidemic.[30] During the Ebola outbreak in Kikwit, five patients were identified who became infected without evidence of any physical contact with any of the patients.[37] Therefore, although the major mode of transmission is through direct contact, transmission through aerosolized particles or vomit cannot be excluded completely. The Ebola virus has been isolated from vaginal and seminal fluids, therefore sexual transmission of Ebola haemorrhagic fever is theoretically possible.[38] The virus also can persist in convalescent patients. Infectious virus was detected in seminal fluid of a convalescent patient, 82 days after onset of the disease,[38] but it remains unknown whether such patients can contribute to transmission.

Treatment

There is no specific treatment for Ebola haemorrhagic fever. Treatment should therefore be symptomatic and focused on providing adequate hydration and nutritional support, antibiotics and antimalaria drugs if needed.[22] During the last phase of the Ebola epidemic in Kikwit, blood transfusions of convalescent patients were given to eight Ebola patients. Seven of them (87.5%) survived.[16] The reason for this low case fatality rate remains unexplained. These patients were transfused relatively late after onset of their symptoms and they therefore already had a better prognosis for survival.[15] Certainly in the last phase of the Ebola epidemic in Kikwit, patients received better care in general: including infusions, antibiotics, antimalarial drugs and food supplementation. Evidence from animal studies indicate that Ebola specific immunoglobulin of equine origin has some activity in suppressing viraemia and delaying disease onset in non-human primates.[39] However, effective treatment of human patients may require antibodies with higher specific activities and more favourable pharmacokinetic properties than the presently available equine immunoglobulins.[40]

Goat immunoglobulins were tested in pre-clinical trials on laboratory animals and were given to researchers suspected of becoming infected with Ebola haemorrhagic fever during their experimental work.[39] It was proposed that these immunoglobulins might be useful for the emergency treatment of persons accidentally infected with Ebola haemorrhagic fever.[39] Guinea pigs were completely protected by injection of hyper immune equine IgG when treatment was initiated early, but not after viraemia had developed.[40] Ebola (subtype Democratic Republic of Congo) virus replication was shown to be inhibited *in vitro* by a series of nine nucleoside analogue inhibitors of S-adenosylhomocysteine hydrolase[41] and carbocyclic 3-deazaadenosine was shown to prevent death in mice infected with the Ebola virus.[41]

Prevalence of Ebola Infection

Ebola seroprevalence studies using the IFA test have shown high seroprevalences in West and Central Africa.[29] Therefore, the hypothesis has been proposed that there could be other Ebola viruses in Africa that are only causing mild or subclinical infections in humans and that are antigenically cross-reactive with the pathogenic Ebola viruses.[42] That such a virus may exist is also suggested by the experience in the U.S.A. with the Ebola Reston virus. During the Ebola Reston type epidemic in the U.S.A., in two of the employees at the quarantine facility evidence of a past infection with low antibody titres was found. None of these employees developed symptoms.[43,44]

In the Central African Republic higher seroprevalence rates were found in hunters, compared with farmers.[45] In a seroprevalence study performed in the Kikwit region, after the epidemic, using a new ELISA test for Ebola viruses, the prevalence of Ebola IgG antibodies was 9.3% among individuals living in villages surrounding Kikwit, compared with 2.2% of individuals living in Kikwit.[29] Both studies confirm the epidemiological evidence from outbreak investigations[1,2,4,5] that the reservoir of Ebola or Ebola like viruses is probably situated in the African forests.

The Ebola Reservoir

Up until now, the primary reservoir of the Ebola virus has not been detected. Non-human primates are certainly not the reservoir because they also become ill when infected and rapidly die as humans do.[46,47] So far, all ecological studies, involving thousands of vertebrates and more than 30 000 invertebrates, have been unable to detect any species infected with the Ebola virus.[48] At the National Institute of Virology in South Africa, a large variety of plants, vertebrates and invertebrates were injected experimentally with the Ebola virus by Swaenepoel.[49] Only bats were found to support replication and circulation of high titres of virus, without developing disease.[49]

During the recent Marburg epidemic in the North East of the Democratic Republic of Congo, a large number of

cases were mine workers working in the gold mines of Durban. These mines are inhabited by a large number of bats and rodents. During the epidemic animals were captured and virological investigations are now ongoing to see whether they harbour the Marburg virus. Because the Ebola and the Marburg virus are both filoviridae, it is possible that the reservoir for both viruses could be found in the same or a closely related species.

The Future

It is likely that new epidemics of Ebola haemorrhagic fever will develop in Africa amplified by nosocomial transmission, as long as universal precautions and barrier nursing techniques are not used. Therefore, health infrastructures should be strengthened. The awareness of Ebola haemorrhagic fever after the Kikwit and Gabon epidemics may decrease over time. The recent Marburg epidemic in the Democratic Republic of Congo was again only detected many months after the first clinical cases.

Surveillance for haemorrhagic fevers should be strengthened in order to detect new epidemics in an early stage.[26] This not only will lead to a more rapid control of the epidemic, but will also allow scientists to identify the index case(s) and to detect the reservoir.

Because of weak health infrastructures, patients occasionally travel to other countries to seek care. Therefore, it is possible that a patient with Ebola haemorrhagic fever could arrive at a hospital, either in an African country where Ebola haemorrhagic fever has never been reported, or in Europe.[50] Also, in Europe physicians should include Ebola haemorrhagic fever in the differential diagnosis of patients with fever returning from Africa. As long as we do not know the reservoir of the filoviridae and as long as the hygienic conditions in many African countries remain so poor, these infections remain a threat to public health.[33]

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