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EBOLA VIRUS DISEASE: A REVIEW ON EPIDEMIOLOGY, PATHOGENESIS, TRANSMISSION AND TREATMENT

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ABSTRACT

West Africa is facing the largest outbreak of Ebola virus disease (EVD) in history. The virus causing this outbreak, the Zaire Ebolavirus (EBOV), belongs to the genus *Ebolavirus* which together with the genus *Marburgvirus* forms the family of the *Filoviridae*. The epidemiology and pathogenesis of Ebola virus disease is presented here, including new knowledge emerging from the 2014-2015 epidemic of Ebola virus disease in West Africa. In the past, Ebola and Marburg viruses were classified as "haemorrhagic fever viruses", based upon their clinical manifestations, which include coagulation defects, bleeding and shock. Ebola virus disease is a severe, often fatal, zoonotic filovirus infection. There are five species: Zaire Ebola virus, Sudan Ebola virus, Tai Forest Ebola virus, Bundibugyo Ebola virus, and Reston Ebola virus. Human to human transmission occurs through contact with body fluids from infected patients. The incubation period after infection is 1- 21 days and patients are not considered infectious until they develop symptoms. However, remarkable progress has been demonstrated by researchers in understanding the pathogenicity of the Ebola virus.

KEYWORDS: Ebola virus disease, Viral haemorrhagic fever, Epidemiology, Pathogenesis, Transmission, Treatment.

INTRODUCTION

Ebola is a viral illness of which the initial symptoms can include a sudden fever, intense weakness, muscle pain, headache, anorexia, myalgia and a sore throat. These signs are soon followed by nausea, vomiting, abdominal pain and diarrhoea. When first examined, the patients are usually overtly ill, dehydrated, apathetic and disoriented.[1] According to the World Health Organization (WHO) airborne transmission of Ebola virus has been

hypothesized but not demonstrated in humans. Ebola is not spread through the air or by water, or in general, by food. However, in Africa, Ebola may be spread as a result of handling bush meat (wild animals hunted for food) and contact with infected bats. The disease infects humans through close contact with infected animals, including chimpanzees, fruit bats, and forest antelope.

Ebola haemorrhagic fever (EHF) is caused by any of five genetically distinct members of the *Filoviridae* family: *Zaire ebolavirus* (ZEBOV), *Sudan ebolavirus* (SEBOV), *Côte d'Ivoire ebolavirus* (CEBOV), *Bundibugyo ebolavirus* (BEBOV) and *Reston ebolavirus* (REBOV). *Côte d'Ivoire ebolavirus* has been associated with only one human case (Le Guenno *et al*. 1995). *Reston ebolavirus* has only caused disease in non-human primates (NHP) and was found in swine suffering from porcine reproductive and respiratory disease syndrome (Barrette *et al*. 2009). Leroy, Gonzalez and Baize (2011) reviewed the major scientific advances in our understanding of the ecology, host interactions, and control of the Ebola and Marburg viruses.[2] In the present review we report important features related to Ebola outbreaks in Africa based on previous findings and own observations during major outbreaks that occurred on the continent. The first outbreak of an unknown infectious disease (Marburg disease) was reported in Germany and Yugoslavia in the year 1967. An estimated 31 persons were affected in which 7 persons died. Eventually, a new strand of the virus was extracted from a patient and was traced back to velvet monkey imported from Uganda.[3] The Ebola virus was identified in the year 1976 and has caused periodic outbreaks in West African countries. The disease has a case fatality rate up to 90%.

Ebola has been classified as a biosafety level four pathogen and there is no currently approved vaccine or treatment for the virus. Ebola haemorrhagic fever is caused by a negative-strand RNA virus. The viral genome encodes seven structural proteins and one non-structural protein (soluble glycoprotein). Morphologically, the virus consists of a linear genome entirely enclosed in an envelope, which is coated by the membrane glycoprotein, organized in homotrimers.

Epidemiology

Ebolavirus and MARV are geographically restricted to and cause outbreaks in sub-Saharan Africa; however, REBOV is found in nonhuman primates and pigs in the Philippines. The first filovirus was discovered in 1967 after an outbreak of Marburg haemorrhagic fever infection in Germany. This infection originated from Cercopithecusaethiops monkeys that

were imported from Uganda. In 1976, the first natural outbreak of ZEBOV occurred in northern Zaı¨re (now called the Democratic Republic of the Congo). In 1976, SEBOV was discovered in an outbreak in Nzara in Sudan.

In 1994, TAFV was discovered in a Swiss biologist who acquired the infection in the Republic of Coˆte d'Ivoire (i.e., the Ivory Coast). In 1989, REBOV was first discovered in monkeys (Macaca fascicularis) that were exported from the Philippines to Reston, Virginia, and USA the infected monkeys were subsequently exported to Italy (1992-1993) and to Texas (1996). Cynomolgus macaques in the Philippines are naturally infected, as are pigs. The REBOV appears to be non-pathogenic to humans.

Ebola haemorrhagic fever has been associated with large human outbreaks, with case fatality rates for ZEBOV as high as 90%. The case fatality rate of EBOV in NHP is unknown but some ecological data suggest that EBOV has contributed to declines of up to 98% of local great ape populations in Gabon and the Republic of Congo (Walsh *et al*. 2003). Currently there are no approved antiviral drugs or vaccines against filoviruses. The prevention of EHF requires improving our understanding of the epidemiology of the disease, especially the role of wildlife, including bats, in the transmission of Ebola virus to humans.

Looking at the 2014 EBOV disease (EVD) outbreak in West Africa, as of September 14, 2014, a total of 4507 probable and confirmed cases, including 2296 deaths from EVD (Zaire species) had been reported from five countries in West Africa: Guinea, Liberia, Nigeria, Senegal and Sierra Leone. The World Health Organization Ebola Response Team analysed a detailed subset of data on 3343 confirmed and 667 probable Ebola cases collected from the five countries and found out that the majority of the patients are 15-44 years of age with 49% male. The case fatality rate was estimated at 70.8% (95% *CI*, 69-73) among persons with known clinical outcome of infection. The course of infection, including signs and symptoms, incubation period and serial interval, is similar to that reported in previous outbreaks of EVD. Assuming no change in the control measures for this epidemic, the team projected that by November2, 2014, the cumulative reported numbers of confirmed and probable cases will be 5740 in Guinea, 9890 in Liberia and 5000 in Sierra Leone, exceeding 20000 in total[2]. In the 2014 outbreak, the World Health Organization conducted a virological analysis to determine if there was any linkage between the EBOV in West Africa and the Democratic Republic of Congo. The epidemiological investigation and results concluded that the outbreaks in the Democratic Republic of Congo were completely separate and independent event from the

cases reported in West Africa. The finding reassures investigators that the virus has not spread from West to Central Africa.

However, investigators have isolated 99 EBOV genomes from infected patients in Sierra Leone. Upon examination of the specimens, investigators concluded that there is rapid mutation of the virus which could have implication for the development of diagnostics, vaccines, and therapies of the EBOV. It was observed that the sequence of the virus has changed since the start of the outbreak and the researchers have not found any additional zoonotic sources of the virus in the outbreak strains. Additionally, it was mentioned that the EBOV can affect approximately 20000 persons before it is contained. Nonetheless, the typical symptoms seen in patients with the EBOV can be mistaken for other infectious diseases that are more common. Nosocomial transmission mainly due to lack of hygiene, is of measure public health concern. Based on experiences of former episodes, isolation of patients and use of strict barrier nursing procedures are sufficient to interrupt transmission.[1]

Pathogenesis

Ebola viruses enter the human body via mucosal surfaces, abrasions and injuries in the skin or by direct parental transmission. Infection through intact skin is considered unlikely, although not excluded. The virus has been successfully isolated from skin (biopsy) and body fluids. Several laboratory associated infections have been reported in the past decades, often after needle accidents or direct contact with infectious materials.

Ebola viruses are biosafety level-4 pathogens and require special containment measures and barrier protection, particularly for health care workers. The viruses can survive in liquid or dried material for many days. They are inactivated by gamma irradiation, heating for 60 minutes at 60^{o} C or boiling for 5 minutes, and are sensitive to sodium hypochlorite (bleach) and other disinfectants. Freezing or refrigeration will not inactivate Ebola viruses. The incubation period (the period between infection and first symptoms) is usually 4 to 10 days but can be as short as 2 days and as long as 21 days. The CFR for ZEBOV infections is estimated to be between 44% and 90%. Ebola viruses are highly transmissible by direct contact with infected blood, secretions, tissues, organs, and other bodily fluids from dead or living infected persons. The principal mode of transmission in human outbreaks is person-to-person transmission through direct contact with a symptomatic or dead EVD case. Airborne transmission has not been documented.[4]

The infection generally involves necrosis of the liver, spleen, kidney, lymph nodes, testes, and ovaries due to viral replication within parenchymal cells. More significant effects are microvascular damage, changes in vascular permeability, and activation of the clotting cascade. Damage to platelets and endothelial cells results in the disruption of fluid balance and homeostasis. Additionally, the virus is believed to compromise and suppress immunologic function.[3] Although the natural reservoir host of Ebola viruses has not yet been identified, the way in which the virus first appears in a human at the start of an outbreak is unknown. However, scientists believe that the first patient becomes infected through contact with an infected animal, such as a fruit bat or primate (apes and monkeys), which is called a 'spill over' event. Person-to-person transmission follows and can lead to large numbers of affected people. In some past Ebola outbreaks, primates were also affected by Ebola and multiple spill over events occurred when people touched or ate infected primates.

Cell entry and tissue damage

After entering the body through mucous membranes, breaks in the skin, or parenterally, Ebola virus infects many different cell types. Macrophages and dendritic cells are probably the first to be infected; filoviruses replicated readily within these ubiquitous "sentinel" cells, causing their necrosis and releasing large numbers of new viral particles into extracellular fluids. Fatal infection is characterized by multifocal necrosis in tissues such as the liver and spleen.

Gastrointestinal dysfunction

Patient with EBD commonly suffer from vomiting and diarrhoea, which can result in acute volume depletion, hypotension and shock.

Systemic inflammatory response

It induces the release of cytokines, chemokines and other pro-inflammatory mediators from macrophages and other cells. Infected macrophages produce tumour necrosis factor- alpha, interleukins- 1 beta and nitric oxide.

Coagulation defects

EBD appear to be induced indirectly, through the host inflammatory response. Virus infected macrophages synthesize cell surface tissue factor, triggering the extrinsic coagulation pathway; pro-inflammatory cytokines also induce macrophages to produce TF.

Impairment of adaptive immunity

Dendritic cells, which have primary responsibility for the initiation of adaptive immune responses, are major site of filoviral replication. Adaptive immunity is also impaired by the loss of lymphocytes that accompanies method Ebola virus infection.

Transmission

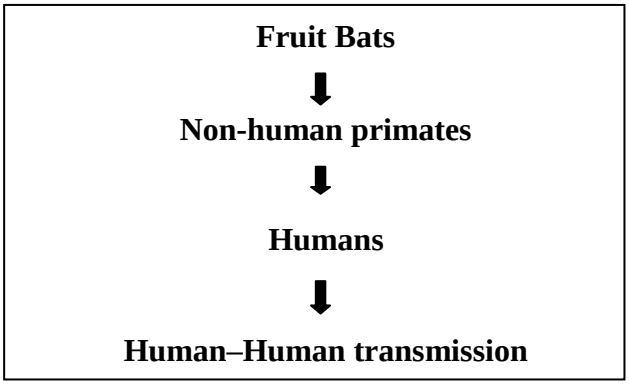

Fig. 1 Transmission of Ebola virus.

In most outbreaks, Ebola virus is introduced into human populations via the handling of infected animal carcasses. In these cases, the first source of transmission is an animal found dead or hunted in the forest, followed by person-to-person transmission from index case to family members or health-care staff. Animal-to-human transmission occurs when people come into contact with tissues and bodily fluids of infected animals, especially with infected nonhuman primates (Leroy *et al*. 2004). Transmission has been reported in Côte d'Ivoire where an ethologist was infected through handling an infected, dead chimpanzee in the Taï Forest (Le Guenno *et al*. 1995). It was confirmed that the deaths of chimpanzees were indeed due to Ebola virus.

Transmission can occur through following ways: Person to person It can occurs through direct contact with blood, body fluids or skin of patients with Ebola virus disease, including those who have died from the infection.

Risk of transmission through different body fluids: Infectious virus has also been detected in urine, saliva, semen, aqueous humour, and breast milk.

Risk of transmission through contact with contaminated surfaces: Ebola virus may be transmitted through contaminated surfaces and objects. The Centres for Disease Control and Prevention (CDC) indicates that virus on surfaces may remain infectious from hours to days.

Risk of air born transmission: Ebola virus released as a small particle aerosol is highly infectious for rodents and nonhuman primates. Healthcare workers may therefore be at risk of Ebola virus disease if exposed to aerosol generated during medical procedures.

Nosocomial Transmission: Transmission to healthcare workers may occur when appropriate personal protective equipment is not available or is not properly used, especially when caring for a severely ill patient who is not recognized as having Ebola virus disease.

Transmission from animals: Contact with infected animals-human infection with Ebola virus can occur through contact with wild animals.

The virus is highly contagious which is transmitted to individuals in direct contact with body fluids from an infected person. The risk of transmission is highest during the latent stage of the disease but the level of transmission decreases during the early stages even if there is a high risk exposure. Persons that are at the greatest risk for infection of the EBOV during an outbreak are, scientists, health care workers, relatives and those in close contact with ill individuals and deceased patients. Basic hygienic practices can be cultivated in the prevention of the EBOV such as regular washing of hands and changing of attire before and after getting in contact with these animals. Moreover, the consumption of sick animals should be avoided.

Treatment

In a clinical experiment conducted late in the 1995 Ebola outbreak in Kikwit, human convalescent blood was used for passive immunisation to treat patients that had been infected naturally with ZEBOV; seven out of eight patients who received blood transfusion from convalescent Ebola patients survived (Mupapa *et al*. 1999). Such experiments, unfortunately, have not been repeated in further outbreaks because *in vitro* studies showed that antibodies against Ebola had no neutralising activities.[5]

EVD is managed with supportive therapy. This consists of balancing the patient's fluids and electrolytes, maintaining their blood circulation, blood oxygen levels, blood pressure and treating any complicating infections.[6] ZMapp is an experimental biopharmaceutical drug made up of three chimeric monoclonal antibodies. The two antiviral drugs (Brincidofovir, Favipiravir) have been approved for trials in West Africa. The initial results for trials are expected by early 2015. It is in developmental phase trials by ZMapp Biopharmaceutical.[7]

CONCLUSION

The Ebola virus disease is significantly affecting a vast majority of persons in West Africa and much progress has been made in the understanding of the EVD replication. Tremendous amount of experiments have been conducted to develop drugs and vaccines which can prevent the spread of this dreadful virus. Animal models such as mice, guinea pigs, hamsters and NHPs have been used to test the effectiveness or safety of the vaccines or drugs developed. Currently treatment strategies rely solely on the early start of supportive care, where aggressive fluid replacement therapy is proven to drastically improve the survival rates. The current EVD outbreak stresses the already weak healthcare and public health systems in the affected countries, but also triggers increased awareness in countries at risk for EVD import cases.

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