

Ebola Virus Infections

Ebola Virüs Enfeksiyonları

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Özet

Ebola, Filoviridae ailesinden, zarflı, segmentsiz, negative polariteli bir RNA virusudur. Ebola virus ilk kez 1976 yılında Sudan ve Zaire'de, kanamalı ateşle seyreden iki salgınla ilişkili olarak tanımlanmıştır. Son zamanlarda, Uganda, Gabon ve Kongo Demokratik Cumhuriyetinde (eski ismi; Zaire) kanamalı ateş ile seyreden büyük epidemiler yaşandı. Bu enfeksiyon, genellikle ateş, titreme, halsizlik, yorgunluk, bitkinlik ve kas ağrıları ile karakterizedir. Ebola virusu ile infekte hastalarda, başlangıçta non-spesifik grip benzeri semptomlar görülmekle birlikte, çoklu organ yetmezliği ve septik şok gelişebilmektedir. Virusun bulaşması, direk olarak hastaların vücut sıvıları yada infekte sekresyonlarla kontamine nesnelere temas sonucu olmaktadır.

Anahtar kelimeler: : Ebola virusu, enfeksiyon

Abstract

Ebola virus belongs to the family Filoviridae, which comprises filamentous, enveloped, nonsegmented, negative-sense RNA viruses. Ebola virus was first described in 1976 in association with two outbreaks of haemorrhagic fever in two neighboring locations: first in southern Sudan and subsequently in Zaire. Recently, Uganda, Gabon and the Democratic Republic of Congo (former Zaire) suffered from large epidemics of viral haemorrhagic fever imputed to Ebola virus. Generally, the infection is characterized by fever, chills, weakness, malaise, and myalgia. Patients with Ebola virus disease initially present with non-specific influenza-like symptoms and can progress to multi organ failure and septic shock. The transmission of the virus is through direct contact with bodily fluids of patients, or exposure to contaminated objects with infected secretions.

Key words: Ebola virus, infection

Introduction

Ebola virus (EBOV) is considered as the prototype pathogen of viral hemorrhagic fever; cause a severe and often fatal hemorrhagic fever in humans and other mammals and high case mortality rates. This high fatality combined with the absence of treatment and vaccination options, makes Ebola virus an important public health pathogen and biothreat pathogen of category A potential bioterrorism agents by the Centers for Disease Control and Prevention (1).

EBOV acquired public notoriety in the last decade largely as a result of the highly disseminated isolation of a new EBOV species in a suburb of Washington, DC, in 1989, together with the dramatic clinical display of EBOV infection and high case-mortality rate in Africa and the unusual and striking morphology of the virus. The evolution in understanding the origins of the path physiological changes that make EBOV infections of humans so destructiveness has been slow, primarily because these viruses require special containment for safe research (2).

Ebola virus infection is associated with a case fatality rate of so high, approaching 90% in some outbreaks depending on the virus species. Specific conditions in hospitals and communities in Africa facilitate the spread of the infections from human to human (3). EBOV infections are usually the most severe of those caused by the viruses of lethal hemorrhagic disease in humans. Clinical symptoms appear suddenly after an incubation period of 2 to 21 days (4).

Epidemiology

Ebola virus was first described in 1976 in association with two simultaneous outbreaks of haemorrhagic fever in two neighboring locations: first in southern Sudan and subsequently in former Zaire, (now the Democratic Republic of the Congo (DRC)). In late August 1979, epidemic haemorrhagic fever recurred in Nzara and was also seen among persons in Yambio, 25 km away (5). An unknown causative agent was isolated from patients in both outbreaks and named Ebola virus. These two epidemics were caused by two distinct species of Ebola virus, Sudan Ebola virus (SEBOV) and Zaire Ebola virus (ZEBOV), a fact not recognized until years later (6).

Ebola virus was morphologically similar to Marburg virus but serologically distinct from it. The outbreak was strongly associated with index cases staff in a single cotton factory in town and spread was to close relative's involved 67 cases. The epidemic was increased by exportation of cases to neighboring areas, at last a third of staff which (41 patients) died (7).

The ZEBOV outbreak included 318 cases and 280 deaths (88% mortality), while the SEBOV outbreak included 284 cases and 151 deaths (53% mortality). Since 1976, EBOV has appeared sporadically in Africa, it was caused several small to mid-size outbreaks between 1976 and 1979. In 1995, there was a large epidemic of ZEBOV haemorrhagic fever including 315 cases, with an 81% case mortality rate, in Kikwit, a community in the former Zaire (5).

Recently, Uganda, Gabon and the Democratic Repub-

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lic of Congo suffered from large epidemics of viral haemorrhagic fever imputed to EBOV. All involved in the outbreak of the Democratic Republic of Congo also a catastrophic decline in the numbers of great apes, which are thought to have a role in the transmission of infection to humans (8).

In 1989, a third species of EBOV, Reston Ebola virus (REBOV), founded in Reston, Virginia, in association with an outbreak of viral haemorrhagic fever among *Cynomolgus* monkeys (*Macaca fascicularis*) imported to the U.S.A. from the Philippines. Hundreds of monkeys were infected (with high mortality) in this episode but no human cases occurred, although four animal caretakers seroconvert without overt disease (9).

Ebola virus remains a scourge for the population of equatorial Africa, with an increase in the numbers of outbreaks and cases since 2000. Almost all patient cases are infected due to the emergence or reemergence of ZEBOV in those regions of Gabon, DRC, and of SEBOV in Sudan and Uganda (10).

On March 10, 2014, hospitals and public health services in Guéckédou and Macenta alerted the Ministry of Health of Guinea and two days later Médecins sans Frontières in Guinea about clusters of a mysterious disease characterized by fever, severe diarrhea, vomiting, and an apparent high fatality rate. In Guéckédou, eight patients were hospitalized; three of them died, and additional deaths were reported among the families of the patients. Several deaths were reported in Macenta, including deaths among hospital staff members. Virologic investigation identified Zaire Ebola virus as the causative agent (3).

The last reported outbreaks (this is the 26th outbreak) began in Guinea in December 2013 and then spread to Liberia, Sierra Leone, Nigeria, Mali, Senegal, Spain, United States, and United Kingdom. As of 21 April 2015, the World Health Organization (WHO) have reported a total of 26,109 suspected cases and 10,835 deaths of the outbreak (table 1), (11, 12).

Table 1. The distribution of the outbreaks of Ebola virus disease reported between December 2013 and 21 April 2015.

Country	Cases	Deaths
Sierra Leone	12,294	3,885
Liberia	10,212	4,573
Guinea	3,568	2,362
Nigeria	20	8
Mali	8	6
United States,	4	1
Senegal	1	0
Spain	1	0
United Kingdom	1	0
Total	26,109	10,835

Taxonomy

EBOV belongs to the family Filoviridae, which comprises filamentous, enveloped, nonsegmented, negative-sense RNA viruses. The family Filoviridae is divided into two genera: Marburgvirus and Ebolavirus, which have likely evolved from a common ancestor. The Marburgvirus genus contains a single species: Lake Victoria marburg virus (LVMARV). Genus Ebola virus comprises five distinct species: Bundibugyo ebolavirus (BDBV), Zaire ebolavirus (ZEBOV), Reston ebolavirus (REBOV), Sudan ebolavirus (SEBOV), and Ivory Coast EBOV (ICEBOV) (3, 13),

while REBOV does not cause disease in humans and the other species have been associated with large human outbreaks of Ebola hemorrhagic fever (14).

Structure and protein functions

Ebola viruses have characteristic filamentous particles that give the virus family its name, which are enveloped, non-segmented, negative sense ssRNA viruses classified by the International Committee on Taxonomy of Viruses as belonging to the genus Ebola virus in the family Filoviridae. Ebola virus particles have a uniform diameter of 80 nm but can greatly vary in length, with lengths up to 14000 nm (15). The EBOV genome, which is approximately 19 kb in length, encodes seven structural proteins: nucleoprotein (NP), virion protein (VP) 35, VP40, VP30, VP24, glycoprotein (GP), RNA-dependent RNA polymerase (L) and 5' trailer (16). With the exception of the (GP) gene, all genes are monocistronic, encoding for one structural protein. The nucleoprotein (NP) is associated with the viral genome and collected into a helical nucleocapsid (NC) along with the polymerase cofactor (VP35), the transcription activator are (VP30) and (L). The viral proteins that involve the NC catalyze the replication and transcription of the viral genome (17). Four of these proteins (NP, VP30, VP35 and L) associate with the genomic RNA in a ribonucleoprotein complex, whereas the three remaining proteins (GP, VP24 and VP40) are associated with the membrane (18, 19).

An important distinction of Ebola virus from other Mononegavirales is the production of a soluble glycoprotein, which is the primary product of the GP gene and that forms spikes on virions and plays a crucial role in virus entry into cells by mediating receptor binding and fusion (20, 21). A minor viral matrix protein, VP24 is also required for NC assembly. If NP is expressed alone in cells, it assembles together with cellular RNA to form a loose coil-like structure. When NP is co-expressed with VP24 and VP35, NC-like structures are formed in the cytoplasm that are morphologically indistinguishable from those seen in infected cells (22).

Ecology

It is believed that the Ebola virus to be zoonotic classic with the continuation of it in a reservoir species and generally found in endemic areas. The monkeys, man, and perhaps other mammalian species that are susceptible to Ebola virus infection are regarded as end hosts and not as reservoir species (23).

Given that apes subject to EBOV infection following an acute disease similar to that in humans, these species are not believed as a classical reservoir species. Thus, following the detection of EBOV in 1976, and again after the 1994 case in Ivory Coast and the 1995 outbreak in DRC, dense efforts were made to identify the natural reservoir; however, neither potential hosts nor arthropod vectors were identified (24, 25).

In a survey carried out on small vertebrates captured through the 2001 and 2003 ZEBOV outbreaks in Gabon/RC found incidence of asymptomatic infection in three species of fruit bats: *Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata* (26). ZEBOV RNA was found in some liver and spleen of animal samples, while in other animals EBOV-specific IgG antibodies were detected in serum, probably indicating that the former group of animals were recently infected and had not yet developed noticeable immune responses. These data support earlier findings that explained replication and circulation of high titers of EBOV in experimentally infected fruit and insectivorous bats in the absence of illness (27). However,

the high titers shown in the experimental bat model raise questions as to why virus isolation has not been achieved from any of the naturally infected bat species, particularly because virus isolation is usually easily achieved for filoviruses from clinical material. Further lends support to the idea of bats as a reservoir species for filoviruses (26).

Infections with Ebola virus are infrequent in equatorial Africa, although perhaps under-reported. Transmission from the reservoir species to man or other end hosts might therefore be an infrequent incidence, given the limited distribution of or limited contact with the reservoir species. But, bats are frequently encountered in equatorial Africa and hunted for food in many places (26).

Clinical manifestations

The diseases caused by Ebola in humans are similar in their clinical manifestations, differing only in severity and case-mortality rate. Patients with Ebola virus disease typically have an abrupt onset of symptoms 8 to 10 days after exposure (range 2 to 21 days) (28). The incubation period for the individual patient depends, in part, upon the type of exposure (e.g., approximately 6 days for percutaneous exposure versus 10 days for contact exposure) (29). The different species of Ebola virus seem to cause somewhat different clinical syndromes, but opportunities for close observation of the diseases under good conditions have been rare. Generally, Ebola virus is characterized by fever, chills, weakness, malaise, and myalgia. Patients with Ebola virus disease initially present with non-specific influenza-like symptoms and can progress to multi organ failure and septic shock (30). Important clinical findings of patients with Ebola virus disease are as follows: (prostration), gastrointestinal signs and symptoms usually develop several days after the initial presentation, these include (anorexia, nausea, vomiting, abdominal pain, diarrhea), respiratory (chest pain, shortness of breath, cough, nasal discharge), vascular (conjunctival injection, postural hypotension, cerebral edema), and neurological (severe headache, confusion, coma) manifestations. Abnormalities in blood coagulation and hemorrhagic manifestations arise during the peak of the illness and include petechiae, ecchymosis/bruising, uncontrolled oozing from venipuncture sites, mucosal hemorrhages, and Frank hemorrhage is less common, and however, massive loss of blood is atypical and, when present, is largely restricted to the gastrointestinal tract. In fact, even in these cases, blood volume loss is insufficient to account for death. Pregnant women may experience spontaneous miscarriages (2, 15, 31, 32).

Pathogenesis

Information about the pathology and pathogenesis of EBOV infections in human is scattered. Understanding the kinetics of host-pathogen relationships and identify the critical pathogenetic processes are important for the development of rational therapeutic interventions. Characterized Ebola virus infection of humans and non-human is primates by lymphopenia and severe degeneration in the lymphoid tissues and defects in the coagulation system (33, 34).

EBOV enters the body during mucosal surfaces, breaks and abrasions in the skin, or by injection. Pathogen infects many types of cells, including monocytes, macrophages, endothelial cells, dendritic cells, fibroblasts, liver cells, adrenal cortical cells, and epithelial cells. Due to the difficulty of conducting clinical studies under the conditions of the outbreak, almost all data on the pathogenesis of EBOV diseases have been obtained from

laboratory experiments using mice, guinea pigs, and a variety of nonhuman primates (35).

Whatever the point of entry into the body, macrophages and dendritic cells are probably the first cells to infection. Filoviruses repeat easily inside these cells, causing necrosis and the release of significant numbers of new viral particles in the extracellular fluid. Spread to sectional lymph nodes results in further rounds of replication, followed by spreading the virus to dendritic cells and macrophages in the liver, spleen, thymus, and other lymphoid tissues. Helped by the rapid spread of systemic oppression caused by virus type I interferon responses. As the disease progresses, the liver cells, adrenal cortical cells fibroblasts, and many other cell types also become infected, leading to extensive tissue necrosis (36). In addition, massive intravascular apoptosis developed rapidly after infection and persisted until death. Available data suggest that T-lymphocytes are deleted mainly by apoptosis in peripheral blood mononuclear cells of fatal cases (37).

As well as the cause of tissue damage and extensive, Filoviruses also to urge the systemic inflammatory syndrome by stimulating the release of cytokines, chemokines, and other pro-inflammatory mediators from infected macrophages and other cells (38, 39).

Recent studies of ZEBOV outbreaks in Kikwit and Gabon have provided some new information on the inflammatory responses during EBOV infections, infected macrophages with ZEBOV produce tumor necrosis factor (TNF)-alpha, interleukin (IL)-2, IL-10, macrophage chemo-tactic protein (MCP)-1, and nitric oxide (NO). These and other substances have also been identified in blood samples from Ebola-infected macaques and from acutely ill patients were reported in fatal cases in Africa (40, 41). In Gabon, the presence of IL-1 β and elevated concentrations of IL-6 in plasma during the symptomatic phase of infection were associated with survival while release of IL-10 and high levels of neopterin and IL-1RA were associated with a fatal outcome (40). Collapse products of necrotic cells also catalyze the release of the same mediators. It is thus the host response to infection, rather than any toxic effect of the virus, that is responsible for the fever, malaise, vasodilatation, increased vascular permeability, hypotension, and shock of EBOV disease (36).

EBOV replicates at an unusually high rate that suppresses the protein synthesis apparatus of infected cells and host immune defenses. Both the adaptive immune and inflammatory systems respond to infection at the same time that some cell types, more specifically macrophages and monocytes, are targets pertaining to disease pathogenesis. This characteristic of the infection was at first suggested by the immunohistochemical localization of EBOV in vivo: mononuclear phagocytes, endothelial cells, and liver cells are The main objectives of the infection (42). The ingredients of the immune system that may protect against EBOV infection have not been outlined. Antibody titers against EBOV GPs are easily detectable in patients World Health Organization (WHO) recover from EBOV infection; but, recently reports have assigned that serum from recovered patients did not consistently protect against infection or exhibit neutralization of virus replication in cell culture. Moreover, passive transfer of antibodies in animal models only delays the initiate of symptoms and does not alter overall survival (43).

The coagulation defects in blood coagulation during EBOV infections are manifested as petechiae, ecchymosed, mucosal haemorrhages, congestion, and uncontrolled bleeding at venipuncture sites. Whereas, heavy losses in the blood are rare and when present, is confined mainly to the digestive system. Even in these cases, The amount of blood lost is not large enough to cause death. Thrombocytopenia, consump-

tion of clotting factors, and increasing concentrations of fibrin degradation products are other indicators of coagulopathy that characterizes infection EBOV. Results from clinical laboratory data strongly suggest that the coagulation abnormalities that occur during human Ebola haemorrhagic fever (44, 45) are generally agree with disseminated intravascular coagulation. The coagulopathy during Ebola haemorrhagic fever can be caused by many factors, especially during the later stages of disease. For example, rapid reductions in plasma concentrations of the natural anticoagulant protein C were recorded during the course of ZEBOV infection of *Cynomolgus* monkeys (46).

Laboratory diagnostic

The laboratory diagnosis is achieved in two ways for EBOV: measurement of host specific immune responses to infection and detection of viral particles, or particle components in infected individuals. Nowadays, RT-PCR, and antigen detection ELISA are the primary assays to diagnose an acute infection (16, 47). Can detect viral antigen and nucleic acid in the blood from day 3 up to 7–16 days after appear of symptoms. For the detection of antibodies generally the most widely used assays are direct IgG and IgM ELISAs and IgM capture ELISA. Can IgM antibodies appear early in the last 2 days of onset of symptoms and disappear between 30 and 168 days after infection. IgG-specific antibodies develop between day 6 and 18 after onset and persist for many years. Is an IgM or IgG titer rise constitutes a strong presumptive diagnosis. Decreasing IgM, or increasing IgG titres (four-fold), or both, in successive paired serum samples are strongly suggest the latter infection (16, 47, 48).

Other diagnosis depending on leukopenia, thrombocytopenia, transaminase elevations, as well as the often observed kidney and coagulation abnormalities in patients who suffer from a disease EBOV (49). Leukopenia usually presents as lymphopenia and is then followed by an elevated neutrophil count, with an increasing proportion of immature forms Immature granulocytes and abnormal lymphocytes, including plasmacytoid cells and immunoblasts were seen in blood smears. Platelet counts are usually in the range of 50,000 to 100,000/ μ L (35). Platelet counts typically reach to very low around day 6 to 8 of disease. Because filoviruses can cause multifocal hepatic necrosis, blood chemistry tests usually demonstrate elevated serum aspartate aminotransferase and alanine aminotransferase levels, with the former typically increasing more than the latter and causes transaminitis. Also prothrombin and partial thromboplastin times are prolonged and Fibrin degradation products are high, harmonious with disseminated intravascular coagulation. These changes are most significant in cases of severe and fatal. Proteinuria is a common finding and renal insufficiency occurs with development of the disease (36).

Transmission

It is believed that the family fruit bats are the natural hosts Pteropodidae Ebola virus. EBOV is offered in humans through close liaison with blood, secretions, organs or other body fluids of infected animals such as the chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found dead or worse, or in the rainforest. In Mayibou, Gabon in 1996, a dead chimpanzee found in the forest was butchered and eaten by 19 people, all of whom became severely ill over a short interval. The usual pattern is seen in the large outbreaks of Ebola virus disease starts with an emphasis of infection that spread to many patients. Infection

occurs in secondary and subsequent close family members or between the medical staff (7, 8).

EBOV then spreads through person-to-person transmission by intimate contact is the main route of infection in human EBOV diseases outbreaks through broken skin or unprotected mucous membranes with the blood, secretions, organs or other body fluids of patients who has developed signs and symptoms of infection, with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. EBOV has also been detected in urine, semen, and breast milk. Patients who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery from infection. Tears and saliva may also harbor the virus (50).

Healthcare workers are at risk of infection if they care for a patient with Ebola Without taking any appropriate preventive measures. As of October 5, 2014, 401 healthcare workers have become infected during the epidemic in West Africa; this is due largely to a lack of personal protective equipment and/or exposure to patients with Ebola virus unrecognized, approximately 60 percent of them have died (51).

Management

The fight against outbreaks good to apply a set of interventions, namely case management, monitoring and contact tracing, a good laboratory service, safe burials and social mobilization. Local community involvement is the key to controlling the outbreak successfully. Outreach of the risk factors Ebola infection and prevention measures that personnel can take is an effective way to reduce human transmission (36). From direct or close contact with people with EBOV symptoms, particularly with their body fluids. They should wear gloves and appropriate personal protective equipment when caring for patients at home. They are required wash your hands regularly after visiting patients in the hospital, as well as after taking care of patients at home. Regardless of the assumed diagnosis, these include fundamental hand hygiene and respiratory hygiene, use of personal protective equipment (The spray to prevent and other contact with infected material) (35).

Case management is based on isolating patients with strict barrier nursing procedures, such as protective clothing and respirators. These procedures have been quickly enough to interrupt transmission in hospital settings in rural areas in Africa. Significant elements for the prevention of the outbreak is the provision of sterile injection equipment, it is notable and tragically missing in Africa, and personal protective equipment to doctors, nurses, and caretakers, Who are at high risk of downturn of infections in hospitals (52, 53). At present, no strategy has proven successful in specific pre-exposure and post exposure treatment of Ebola virus infections in men.

Treatment and vaccines

There are no known effective treatments for human Ebola virus disease. At this time, treatment of patients with EBOV consists mainly of intensive supportive care. Progress has been mortgaged to the development of treatments / treatment in the first place because these viruses require special containment (Biosafety Level 4) for safe research, but also as a result of the sporadic and transitory nature of EBOV outbreaks (2). Supportive welfare-rehydration with oral or intravenous fluids and treatment of specific symptoms, improves survival. There is as yet no confirmed treatment available for Ebola virus disease. Nevertheless, a group of

potential therapies including blood products, immune therapies and drug therapies are currently being evaluated. Not yet available licensed vaccines, however two potential vaccines are being tested human safety (28).

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