THE EBOLA VIRUS DISEASE IN AFRICA

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Abstract
Ebola virus disease is one of the most deadly human viral diseases in the world, and is caused by the Ebola virus. The symptoms which include (fever, sore throat, muscle pains, headaches, nausea, vomiting and diarrhea), begins usually after infection 2 to 21days. The strains include the Zaire, Sudan, Ivory Coast, and Bundibugyo and Reston. The disease is zoonotic (affects human and non-human primate) and typically occurs in tropical regions. The most recent outbreak of Ebola disease occurred in the year 2014 in Liberia and spilled to Nigeria through late Patrick Sawyer at Lagos. The virus can be acquired upon contact with blood or body fluid of an infected human and animal. The Pathological effect of the virus on infected human is achieved through viral Protein (VP) produced by gene 35 of the virus. The protein interferes with the activation of interferon, a component of human body defenses, thereby hindering protective immune response. Diagnosis is by screening blood samples through ELISA and RTPCR for possible detection of the virus. There is no specific drug for the treatment of Ebola virus disease. Therefore, samples from suspected carriers should be handled with caution.

Keywords: Ebola virus, Disease, Interferon, viral Protein (VP), Strains.

Introduction

Ebola virus is a non-segmented, negative-sense, single-stranded RNA virus that resembles rhabdoviruses and paramyxoviruses in its genome organization and replication mechanisms. It is a member of the family Filoviridae, taken from the Latin "filum," meaning thread-like, based upon their filamentous structure. The family Filoviridae consists of three genera, the Ebola Cueva and Marburg viruses, which are among the most virulent pathogens in humans and primates (Feldmann & Geisbert, 2011). The genus Ebola virus is divided into five species; Zaire, Sudan, Ivory Coast (Tai forest), Bundibugyo, and Reston (Martinni & Siegert, 1971; Bray, 2003). In the past, Ebola and Marburg viruses were classified as "hemorrhagic fever viruses", based upon their clinical manifestations, which include coagulation defects, bleeding, and shock (Bray, 2005). However, the term "hemorrhagic fever" is no longer used to refer to Ebola virus disease since only a small percentage of Ebola patients actually develop significant hemorrhage, and it usually occurs in the terminal phase of fatal illness, when the individual is already in shock (Bray, 2003).

Epidemiology

Ebola virus, was first recognized when two outbreaks occurred in Zaire and in Sudan in 1976 (Feldmann & Giesbert, 2011). Outbreaks of Ebola virus disease have been confined to SubSaharan Africa. An epidemic caused by the Zaire strains, affected 315 people in 1995 in Kikwit, Democratic Republic of Congo. The Sudan strain of the virus infected more than 425 people in Gulu, Uganda in 2000. The 2014-2015 Ebola epidemic, caused by the Zaire strain of the virus, is not only the first to occur in West Africa, but is far larger than all previous outbreaks combined (Baize et al., 2014). In addition to causing human infections, Ebola virus has also spread to wild nonhuman primates, apparently as a result of their contact with an unidentified reservoir host (possibly bats) (Leroy et al., 2004). This has contributed to a marked reduction in chimpanzee and gorilla populations in Central Africa, and has also triggered some human epidemics due to handling of

and/or consumption of sick or dead animals by local villagers as a source of food (Leroy et al., 2004).

The recent outbreak of Ebola virus disease that occurred in Central Africa, an epidemic that began in Guinea in the late 2013, was confirmed by the World Health Organization in March, 2014 (Baize et al., 2014). The initial case was a two-year-old child who developed fever, vomiting, and black stools, without other evidence such as hemorrhage (Baize et al., 2014). The outbreak subsequently spread to Liberia, Sierra Leone, Nigeria, Senegal and Mali (WHO, 2014). Sequence analysis of viruses isolated from patients in Sierra Leone indicated that the epidemic resulted from sustained person-to-person transmission, without any trace of additional introductions from animal reservoirs (Gire et al., 2014).

As at April, 2015, the cumulative number of probable, suspected, and laboratory-confirmed cases attributed to Ebola virus was 26,079 including 10,823 deaths (WHO, 2015). These cases include over 850 infected healthcare workers, of whom approximately 60 percent have since died of the disease (WHO, 2015). The magnitude of the outbreak, especially in Liberia and Sierra Leone was underestimated, due to the fact that individuals with Ebola virus disease were cared for outside the hospital setting (WHO, 2015).

In areas of West Africa where transmission was limited (Senegal, Nigeria and Mali), the disease appeared to have been eliminated (WHO, 2015). In areas of widespread transmission, the rate of new infections was reduced. This laudable achievement was as a result of the introduction of infection control measures in hospitals and funerals, as well as the use of Ebola treatment units and community care centers that assisted in isolating patients with suspected or confirmed cases of Ebola virus disease (Faye et al, 2015).

Transmission

Epidemics of Ebola virus disease are generally thought to begin when an individual becomes infected through contact with the meat or body fluids of an infected animal. Once the patient becomes ill or dies, the virus then spreads to others who come into direct contact with the infected individual's blood, skin, or other body fluids. Studies in laboratory primates have found that animals can be infected with Ebola virus through droplet inoculation of virus into the mouth or eyes suggesting that human infection can result from the inadvertent transfer of virus to these sites from contaminated hands (Jaax et al., 1996).

Prior to the 2014-2015 epidemics in West Africa, outbreaks of Ebola virus disease were typically controlled within a period of weeks to a few months. This outcome was generally attributed to the fact that most outbreaks occurred in remote regions with low population density, where residents rarely traveled far from home. However, the 2014-2015 West African EVD epidemic revealed that Ebola virus disease can spread rapidly and widely as a result of the extensive movement of infected individuals (including undetected travel across national borders), the spread of the disease to densely populated urban areas, inadequate protective measures and the avoidance of medical isolation centers (WHO, 2014).

Person-to-person transmissions occur through direct contact with infected blood, body fluids, or skin of infected person including dead body of diseased patient. The ritual washing of Ebola victims at funerals, played a significant role in the spread of infection in past outbreaks, and has contributed to the epidemic in West Africa. The early phase of the 2014-2015 West African epidemic, several hundred African doctors and nurses became infected while caring for patients with Ebola virus disease an indication that healthcare workers are at high risk of infection, if they do not use appropriate protective measures (Jaax et al., 1996).

The likelihood of infection depends, in part, upon the type of body fluid to which an individual is exposed and the amount of virus it contains (WHO, 2014). Transmission is most likely to occur through direct contact of broken skin or unprotected mucous membranes with virus-containing body fluids from an infected person. According to the World Health Organization (2014), the most infectious body fluids are blood, feces, and vomit. However, Ebola virus can be detected in urine, semen, saliva, and breast milk. Reverse-transcription-polymerase chain reaction (RT-PCR) technique has been reported to have detected Ebola virus RNA in tears and sweat, suggesting the presence of the virus (Kreuels et al 2014).

Pathogenesis

The difficulty of performing clinical studies under outbreak conditions has hindered the generation of complete data on the overall pathogenesis of EDV under laboratory conditions. However, case reports and large-scale observational studies of patients in the 2014-2015 West African outbreak has provided urgently needed data on the pathogenesis of the disease in humans (Lyon et al.,2014; Chertons et al., 2014).

After entering the body through mucous membranes, broken skin, or parenterally, Ebola virus infects many different cell types. Macrophages and dendritic cells are probably the first to be infected; filoviruses replicate readily within these ubiquitous "sentinel" cells, causing their necrosis and releasing large numbers of new viral particles into extracellular fluid (Bray and Geisbert, 2005). The major pathological effect induced to the human body by Ebola virus is a result of the suppression of Type1 Interferon.

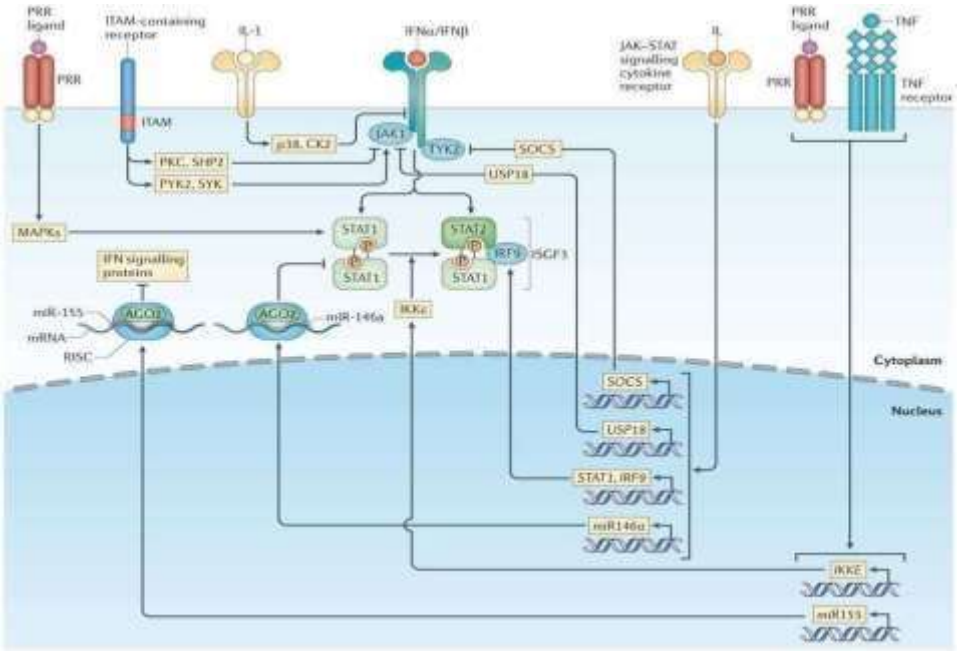

Figure 1: Pathway of how Ebola virus suppress type I interferon responses (Source: Lionel & Laura, 2014).

Various receptor pathways cross-regulate the type I interferon (IFN) response; this alters the expression levels and activation states of IFN signaling components. Various mitogen-activated protein kinase (MAPK)-activating pathways, such as those induced by pattern- recognition

receptors (PRRs), enhance signal transducer and activator of transcription 1 (STAT1) transcriptional activity through phosphorylation of a conserved carboxy-terminal serine (Lionel & Laura, 2014).
Low-level basal signalling by immunoreceptor tyrosine-based activation motif (ITAM)-containing receptors also augments Janus kinase 1 (JAK1) activity through activation of spleen tyrosine kinase (SYK) and protein tyrosine kinase 2 (PYK2). Conversely, strong activation of ITAMcontaining receptors by high-avidity cross linking suppresses IFNα receptor (IFNAR) signalling via protein kinase C (PKC)-mediated recruitment of SH2 domain-containing proteintyrosine phosphatase 2 (SHP2), which dephosphorylates signalling intermediates. Cytokine signalling pathways, including the interleukin-1 (IL-1) pathway, inhibit type I IFN responses by directly promoting IFN receptor turnover via p38 kinase and casein kinase II (CK2) (Lionel & Laura, 2014).

Various cytokines that signal through JAK–STAT pathways, including type I IFNs, regulate the expression levels of both positive and negative regulators of the IFN response pathways. JAK–STAT-induced positive regulators include STAT1 and IFN-regulatory factor 9 (IRF9), whereas negative regulators include the suppressor of cytokine signalling (SOCS) protein family and ubiquitin carboxy-terminal hydrolase 18 (USP18). Inhibitor of NF-κB kinase-ε (IKKε)-mediated STAT1 phosphorylation inhibits STAT1 homodimerization, thereby promoting activation of the IFNstimulated gene factor 3 (ISGF3) complex rather than STAT1 homodimers in response to type I IFN. IKKε expression is induced by various pathways, including tumour necrosis factor (TNF)- and PRR-induced pathways. MicroRNAs induced by cytokine and PRR pathways downregulate the expression of IFN response signalling proteins: for example, miR-146a suppresses STAT1 expression, and miR-155 causes a collective reduction in various IFN signalling proteins. AGO2, Argonaute 2; RISC, RNA-induced silencing complex (Lionel & Laura, 2014).

Dissemination to regional lymph nodes results in further rounds of replication, followed by spread through the bloodstream to dendritic cells and fixed and mobile macrophages in the liver, spleen, thymus, and other lymphoid tissues. Necropsies of infected animals have shown that many cell types (except for lymphocytes and neurons) may be infected, including endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, and epithelial cells. Fatal infection is characterized by multifocal necrosis in tissues such as the liver and spleen (Lionel & Laura, 2014).

Gastrointestinal dysfunction — Patients with Ebola virus disease commonly suffer from vomiting and diarrhea, which can result in acute volume depletion, hypotension, and shock (Bwaka et al.,1997) It is not clear if such dysfunction in Ebola virus disease is the result of viral infection of the gastrointestinal tract, or if it is induced by circulating cytokines, or both. In addition to causing extensive tissue damage, Ebola virus also causes a systemic inflammatory syndrome by inducing the release of cytokines, chemokines, and other proinflammatory mediators from macrophages and other cells (Bray & Geisbert, 2005)

Infected macrophages produce tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6, macrophage chemotactic protein (MCP)-1, and nitric oxide (NO) (Hensley et al., 2002). These and other substances have also been identified in blood samples from Ebola-infected macaques and from acutely ill patients in Africa (Hutchinson & Rollin, 2007) Breakdown products of necrotic cells also stimulate the release of the same mediators (Hutchinson & Rollin, 2007).

This systemic inflammatory response may play a role in inducing gastrointestinal dysfunction, as well as diffuse vascular leak and multiorgan failure that is seen later in the disease course (Bray & Mahanty, 2003).

Ebola virus acts both directly and indirectly to disable antigen-specific immune responses. Dendritic cells, which have primary responsibility for the initiation of adaptive immune responses, are a major site of filoviral replication. In vitro studies have shown that infected cells fail to undergo maturation and are unable to present antigens to naive lymphocytes, potentially explaining why patients dying from Ebola virus disease may not develop antibodies to the virus (Baize et al., 1999)

Adaptive immunity is also impaired by the loss of lymphocytes that accompanies lethal Ebola virus infection (Baize et al., 1999)**.** Although these cells appear to remain uninfected, they undergo "bystander" apoptosis, presumably induced by inflammatory mediators and/or the loss of support signals from dendritic cells. A similar phenomenon is observed in septic shock (Geisbert et al., 2003). However, one study has shown that at least in Ebola-infected mice, virusspecific lymphocyte proliferation still occurs despite the surrounding massive apoptosis, but it arrives too late to prevent a fatal outcome (Bradfute et al., 2008) Discovering ways to accelerate and strengthen such responses may prove to be a fruitful area of research.

Signs and Symptoms

Common signs and symptoms reported from the 2014-2015 West African outbreak include fever, fatigue, headache, vomiting, diarrhea, and loss of appetite (Mahanty and Bray, 2004). Reports have also described weakness, myalgias, as well as a high fever accompanied by relative bradycardia as seen in typhoid fever. Others include:

(i) Gastrointestinal signs and symptoms are common, and usually develop within the first few days of illness. These include watery diarrhea, nausea, vomiting, and abdominal pain. During the 2014-2015 West African outbreak, vomiting and diarrhea have resulted in severe fluid loss, potentially leading to dehydration, hypotension, and shock (Johnson, 1977).

(ii) Despite the traditional name of "Ebola hemorrhagic fever", major bleeding is not a common finding. Reports from the 2014-2015 outbreak in West Africa indicated that only approximately 20 percent of patients have unexplained hemorrhage, most commonly manifested as blood in the stool (about 6 percent), petechiae, ecchymoses, oozing from venipuncture sites, pregnancy related hemorrhage, and/or mucosal hemorrhage (Towner et al.,2008) Major bleeding is seen most commonly in the terminal phase of illness.

(iii) Patients may develop a syndrome suggestive of meningoencephalitis, with findings such as an altered level of consciousness, stiff neck, and/or seizures. These clinical manifestations present later in the course of disease, typically after day 10 (Johnson, 1977).

(iv) Proteinuria is a common finding, and renal insufficiency with elevated blood urea nitrogen and creatinine occurs with progression of illness (Mahanty et al., 2004). When these findings occur early in the course of illness, they are largely due to excessive fluid loss from diarrhea (WHO, 2014).

Guide for Proper Diagnosis

Although there are no therapies specific for Ebola virus disease, it is essential to make the diagnosis as early as possible, in order to initiate supportive measures before the development of irreversible shock and to institute infection control procedures. Thus, providers should ask patients presenting with fever and/or other symptoms consistent with Ebola virus disease if they have travelled to the epidemic area or had contact with a patient with possible Ebola virus disease within 21 days prior to the onset of symptoms (Green, 2014). The following should be noted:

(i) Whether Ebola virus disease is initially considered in the differential diagnosis of a patient with fever and flu-like symptoms will vary markedly with the circumstances. In the setting of the current 2014-2015 epidemic, there is a heightened level of suspicion, both in local

residents and in healthcare workers returning from West Africa to their home countries (Green, 2014).

(ii) However, clinicians should remember that the acute onset of a febrile illness in a person who lives in, or has recently been in West or Central Africa can result from a variety of local infectious diseases, including malaria and other causes of fever, such as Lassa and Marburg viruses (Green, 2014).

(iii) The approach to evaluating patients with possible Ebola virus disease depends upon whether or not the individual displays appropriate signs and symptoms, how likely it is that the exposure will result in disease (ie, the level of risk), and when the exposure occurred (Green, 2014).

(iv) Patients who present with signs and symptoms consistent with Ebola virus disease (fever and/or severe headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage) should be immediately assessed to determine their risk of exposure to Ebola virus (Green, 2014).

(v) By comparison, asymptomatic individuals who have had a possible exposure to Ebola should be monitored so that they can be isolated if signs or symptoms occur; additional restrictions may also be required, depending upon the type of exposure (Green, 2014).

(vi) The specific triage system and type of personal protective equipment (PPE) used during the initial assessment of a patient with possible Ebola virus disease may vary depending upon the setting (eg, emergency department, ambulatory clinic), risk of transmission in the community and the patient's clinical symptoms (Peterson et al., 2004) As examples, medical facilities, especially those in areas with widespread Ebola transmission, should designate areas for screening patients (WHO, 2014). In addition, the types of PPE that are recommended for healthcare personnel caring for a patient whose condition is associated with a high risk of direct contact with body fluids (eg, presence of vomiting, diarrhea, bleeding) are different from those used when evaluating a patient who does not present a hazard due to body fluid exposure (WHO, 2014). In all settings, only essential personnel who are trained in proper donning and removal of PPE should interact with the patient. A more detailed discussion on infection control precautions is found below (WHO, 2014).

Prevention of Ebola Virus Infection

There is no approved vaccine available for Ebola. Travelers to areas affected by EVD outbreak should make sure to:

i. Practice careful hygiene. For example, they should wash your hands with soap and water or an alcohol-based hand sanitizer.
ii. Avoid contact with blood and body fluids and should not handle items that may have come in contact with an infected person’s blood or body fluids (such as clothes, bedding, needles, and medical equipment).
iii. They should avoid funeral or burial rituals that require handling the diseased EVD patients. They should avoid contact with bats and nonhuman primates or blood, fluids, and raw meat prepared from these animals.
iv. They should avoid facilities in West Africa where Ebola patients are being treated. Returned travelers from Ebola affected areas should monitor their health for 21 days at least.

reatment of Ebola Virus Disease

There is currently no approved drug(s) for the treatment EVD (e.g., antiviral drug) of Ebola. Symptoms and complications are treated as they appear. The following basic interventions, when used early, can significantly improve the chances of survival:

- Providing intravenous fluids and balancing electrolytes (body salts)
- Maintaining oxygen status and blood pressure
- Treating other infections if they occur.

Experimental treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness. Recovery from Ebola depends on good supportive care and the patient's immune response. People who recover from Ebola develop antibodies that last for at least 10 years, possibly longer. It is not known if people who recover are immune for life or if they can become infected with a different species of Ebola. Some people who have recovered from Ebola have developed long-term complications, such as joint and vision problems (WHO, 2014).

Conclusion

Ebola virus disease remains a deadly disease that up till now has no cure. The Zaire species of Ebola virus, the causative agent of the 2014-2015 West African epidemics, is among the most virulent human pathogens known. The case-fatality rate in past outbreaks in Central Africa ranging from 80 to 90 percent, and has been reported to be as high as 70 percent in West Africa. The 2014-2015 West African epidemics are the largest filo virus outbreak on record. It started in the nation of Guinea in late 2013 and was confirmed by the World Health Organization in the year 2014. The countries with widespread transmission include Guinea, Liberia, and Sierra Leone. Cases of Ebola virus disease have occurred in hundreds of healthcare workers who were infected while caring for patients. The reservoir host of Ebola virus is not known. Evidence is accumulating that various bat species may serve as a source of infection for both humans and wild primates (WHO, 2014).

Recommendations

i. Awareness should be intensified by governments at all levels and nongovernmental organization on the possible risk factors and routes of transmission of the disease.
ii. Government at all levels should collaborate with WHO to aid the successful development of a candidate vaccine for ebola virus, even Lassa and Marburg viruses.
iii. Health care centers should be aware of the possible transmission of the virus.
iv. The use of hand sanitizers should be encouraged in an area previously affected by ebola virus disease.
v. Quarantine of individuals moving out of ebola affected region should be enforced.

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