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EBOLA VIRUS DISEAES (EVD)

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ABSTRACT

Since the first reported outbreak of Ebola in 1976, there have been approximately 25 outbreaks all of which, except two, have been reported only in east and central Africa. The current outbreak and a single case reported in 1994 in Ivory Coast are the only two outbreaks in West Africa (7). However, the current outbreak, which stared in Guinea (Bissau) in March 2014, remains the deadliest today and the epidemic is still ongoing. New cases are reported daily, particularly in Liberia. This outbreak is unprecedented in many ways. It is the most persisting, lasting more than five months. The spread is across nations and has the largest number of victims. Close to 1500 individuals are dead and very close to 3000 people are infected. More doctors and nurses and other health care workers are infected when compared with previous outbreaks. Over 240 healthcare workers are infected with more than 120 deaths (7). This outbreak also has the least fatality when compared to previous outbreaks. So far, 47% of those infected survive the disease. This work outlines the previous outbreaks and gives a brief summary of current knowledge about EVD.

INFECTIONS DE VIRUS D'EBOLA (VEB)

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RESUME

Depuis le premier cas d'épidémie rapporté en 1976, il y a eu environ 25 foyers épidémiques tous, excepté deux, ont été signalés seulement en Afrique orientale et centrale. L'épidémie actuelle et un seul cas rapporté en 1994 en Côte d'Ivoire sont les deux seuls foyers épidémiques d'Afrique de l'Ouest.Cependant, l'épidémie actuelle reste la plus meurtrière à ce jour et l'épidémie est toujours en cours. Des nouveaux cas sont signalés chaque jour, particulièrement au Libéria. Cette épidémie est sans précédent à bien des égards. Elle est la plus persistante, durant plus de cinq mois. La propagation est entre les nations et a le plus grand nombre de victimes. Près de 1500 personnes sont mortes et près de 3000 personnes infectées. Plusieurs médecins et infirmiers et autres travailleurs de santé sont infectés par rapport aux épidémiesprécédentes. Plus de 240 travailleurs de santé sont infectés avec plus de 120 décès. Cette épidémie a également le moins de décès par rapport aux épidémies précédentes. Jusqu'à présent, 47% de personnes infectées survivent à la maladie. Ce travail présente les épidémies précédentes et donne un bref résumé des connaissances actuelles sur les infections de virus d'Ebola.

INTRODUCTION

Ebola virus disease is caused by Ebola Virus which was identified in 1975 near the Ebola river valley in Zaire during an outbreak in that country. Since 1976, frequent outbreaks have been reported in parts of central and East Africa. Ebola virus is an aggressive pathogen that causes hemorrhagic fever considered one of the most lethal. The mortality rate ranges from 50 to 90%. Outbreaks have been confined to central and East Africa until March of this year when cases were initially reported in Guinea, then Sierra Leone, Liberia and just recently in Nigeria. This is the first time Ebola virus disease outbreaks have been reported outside East and Central Africa. This West African outbreak is the largest outbreak in history and also the most persistent killing more than 1000 people as of today. Also, the number of cases from the current outbreak, which is ongoing, exceeded the number from all previous outbreaks put together. The most worrisome, is the reported cases in Lagos because of the huge population of that city. Lagos population is almost as large of those of Guinea, Sierra Leone and Liberia all together.

EPIDEMIOLOGY

All the outbreaks since 1976 were in central and east

Africa except the lone death in Cote d'Ivoire in 1994. I don't have the details of that single case in Cote d'Ivoire (Table 1). It may be related to an outbreak in that happened about the same time in Gabon. And indeed, that single case may represent the origin of current West African outbreak. We may never know. Out of the 25 reported outbreaks since 1976, only the current epidemics probably originated from West Africa. To date, this outbreak represents the most lethal involving four countries across West Africa.

TABLE 1: CHRONOLOGY OF PREVIOUS EBOLA VIRUS DISEASE OUTBREAKS

Year	Country	Ebolavirus species	Cases	Deaths	Case fatality
2012	Democratic Republic of Congo	Bundibugyo	57	29	51%
2012	Uganda	Sudan	7	4	57%
2012	Uganda	Sudan	24	17	71%
2011	Uganda	Sudan	1	1	100%
2008	Democratic Republic of Congo	Zaire	32	14	44%
2007	Uganda	Bundibugyo	149	37	25%
2007	Democratic Republic of Congo	Zaire	264	187	71%
2005	Congo	Zaire	12	10	83%
2004	Sudan	Sudan	17	7	41%
2003 (Nov-Dec)	Congo	Zaire	35	29	83%
2003 (Jan-Apr)	Congo	Zaire	143	128	90%
2001-2002	Congo	Zaire	59	44	75%
2001-2002	Gabon	Zaire	65	53	82%
2000	Uganda	Sudan	425	224	53%
1996	South Africa (ex-Gabon)	Zaire	1	1	100%
1996 (Jul-Dec)	Gabon	Zaire	60	45	75%
1996 (Jan-Apr)	Gabon	Zaire	31	21	68%
1995	Democratic Republic of Congo	Zaire	315	254	81%
1994	Cote d'Ivoire	Taï Forest	1	0	0%
1994	Gabon	Zaire	52	31	60%
1979	Sudan	Sudan	34	22	65%
1977	Democratic Republic of Congo	Zaire	1	1	100%
1976	Sudan	Sudan	284	151	53%
1976	Democratic Republic of	Zaire	318	280	88%

Figure 1. Obtained from WHO Fact sheet on EVD at www.who.org. Retrieved Aug, 25th , 2014.

VIROLOGY

Ebola Virus is closely related to the Marburg virus, and they both belong to ***Filovideae*** family. The familyname came from their characteristics thread-like appearance. (*filo* is Latin word for filament) This unique morphology provides easy identification on clinical samples using electron microscope. Filoviruses are elongated structure of about 80 nm in diameter. The length of the replicate form is about 970 for Ebola. Ebola nucleocapside is about 50nm and helical in nature and surrounded by a membrane consisting of many projecting spikes. The genome consists of seven open reading frames, which encode structural proteins such as the virion envelope protein or GP, nucleoprotein or NP, matrix proteins VP24 and VP40. There are other none structural proteins such as the VP30 and VP35(3). It also contains other proteins such as the polymerase enzyme.All filoviruses have multiple copies of a single membrane attached glycoprotein(GP), which project from the viral envelope (1,3 4). But unlike the other filoviruses such as the Marburg, Ebola GP open reading frame of Ebola has two gene products; a soluble 60- to 70 kDA protein called sPG and another full length 150- to 170 kDA protein which is directly inserted into the viral memebrane(2). The Ebola virus GP is a good target for multiple neutralizing antibodies (1). In fact, a few have been tested in none-humans and found to be effective in inducing the production of neutralizing antibodies (1).


Photomicrograph of Ebola virus ***credits: streamafrica.com***

CLASSIFICATION

Ebola and Marburg viruses are members of the ***Filoviridae*** family and are pleomorphic negative-sense RNA viruses. Their genomic structure is closely related to those of ***Paramyxoviridae***. There are five identified strains of Ebola virus of which three are known human pathogens. They are, Zaire, Ivory Coast (Bundibugyo) and Sudan strains. Sudan strain is considered the most lethal (3). The fourth and the fifth subtypes called the Reston and Tai forest respectively are yet to be associated with epidemics. Reston subtype was discovered in Reston Virginia in the United States in 1989-1991 from dying cynomolgus monkeys imported from the Philippines. There are episodes of human infections with this strain but with no medical consequences

PATHOGENESIS

The exact manner in which Ebola virus produces EVD is yet to be fully understood. However, it is known that viraemia persists throughout the acute period. When viraemia disappears, patients are normally well and antibodies appear in the patient blood (7). Therefore, it is assumed that the effective immunity response is not humoral. Monocytes, macrophages, and dendritic cells are the early targets of the virus (4). The destruction of these cells play a central role because proinflammatory and antiviral cytokins such as IFN-α, Interlukins, IL, 1,6,8, and 12, tumor necrosis factor, TNF family members and coagulations factors 11, and 13-18 blood levels are markedly increased (4). Extensive viral replication is seen in most of the major organs as well as in cells of the endothelia, epithelia and monocytes lineage of infected individuals and primates. There is severe dysregulation of the vascular and inflammatory response, which play a key role in EVD manifestations.

It has been demonstrated that EBV suppresses host antiviral response, including the Toll-like receptor, (TLR). Interferon (IFN), regulatory factor-3, and protein kinase R (PKR)- mediated pathway in human hepatocytes (4). Also, it was found that when EBV particles attaches itself and enter human macrophages, that resulted in induction of proinflammatory mediators such as IL-6, IL-8 and tumor necrotic factor alpha (TNF-α) (4)

The EBV GP is fingered in some of the cell destructions and the pathogenesis. GP appear to bind preferentially to endothelial cells. The exact receptors for cell binding and infection are not understood (4). There are two types of GP, secreted and transmembrane or sGP. GP allows the virus to introduce its contents to monocytes and macrophages, which leads to cell damage and the release of cytokins. This in turn leads to inflammation and fever. GP also allows the attachment to endothelial cells causing the vascular damages and the subsequent bleedings. Secretary GP or sGP is thought to inhibit neutrophils which would have assisted in viral clearance (4).

IMMUNOLOGY

Immune response to EBV is initially poor because the virus replication is so fast such that the protein synthesis of the infected cell is overwhelmed. The exact component of the immune system that protects against EBV infection is yet to be defined. Protection from serum of convalescent patients has not been found to be consistent. Besides, serum from survivals has not consistently altered the progress of the disease in clinical practice (4). However, a recent study (4) suggests that mononuclear antibody from bone marrow of recovered patients has been shown to confer immunity in murine model of Ebola infection (4).

Cell mediated immunity is thought to play a significant role, but the method is yet to be elucidated. Cytotoxic T lymphocytes are known to provide protection against intracellular organism such as EBV, but their role in EBVD is not well defined. Wilson et al (2000) vaccinated mice with Venezuelan equine encephalopathy virus replicons encoded with EBV NP and then injected the mice with a lethal dose of EBV. The mice survived and they noticed induced antibodies to EBV NP and Major Histocompatibility Complex class-1 restricted CTL (4). This has not been repeated in any other animals but it may provide future clues about the role of CTL in EBOV protection.

TRANSMISSION

Ebola virus disease is a zoonotic diseases and introduction into human population is generally through human contact with blood, feces, secretions, organs or body fluids of infected animals. Consumption of infected bush meats particularly those of apes are thought to be one of the main contact methods. Handling of infected chimpanzees, monkeys, gorillas, antelopes, porcupines and fruits bats is considered the major epidemic sources in Africa.

After the initial infection from animal source, community spread is from human-to-human contacts. Body fluids, blood and indirect contact with the environmental objects that are previously contaminated with infected fluids. Sometimes transmission may be at burial ceremonies where the living have direct contacts with the dead. Recovered men are capable of transmitting the virus up to six months after recovery (4,7).

Health care workers are at a greater risk of acquiring the disease while treating infected individuals. In fact, *I just heard the news from CNN at this moment that the current epidemics has affected 240 health care workers of which about 120 healthcare personnel are dead (CNN, international News Report, 26/8/2014).

CLINICAL PRESENTATION

EVD is an acute severe illness with sudden onset characterized by fever, intense fatigue, myalgia, headache and sore throat (1, 2, 4, 5.8, 9). Incubation period is from two to 21 days. There may be nausea and vomiting with abdominal cramps mimicking several other tropical illnesses. Diarrhea, cough and chest pain may complicate the diagnostic approach. Other common features are pharyngitis, photophobia, internal and external bleeding from the mouth, ears and nose. There may be blood in sputum and urine. CNS involvement, lymphadenophathy, jaundice and pancreatitis are not uncommon. A prominent maculopapular rash around the trunk is commonly seen around the 5th day. Wasting and bleeding manifestations are also common about the same time. By the second week, patient either begins to show marked improvement or die from multiorgan dysfunctions (9). Survivors may be left with orchitis, recurrent hepatitis, transverse myelitis or uveitis (9) Mortality from EVD may be as high as 90% but in general, Zaire subtype is the most lethal.

DIAGNOSIS

The following diseases must be excluded before EVD is considered, particularly in a tropical setting; malaria, typhoid fever, shigellosis, cholera, leptospirosis, plague, rickettsiosis, relapsing fever, meningitis, hepatitis, and other viral hemorrhagic fevers like yellow fever and Marburg virus disease (7). During epidemics, healthcare workers must practice universal precautions when attending to all patients.

Laboratory diagnosis rests on identification of the virus, its genetic markers or the viral antigen. Real-time PCR is one of the strong diagnostic tools today because of speed and specificity. Cell culture, when possible may be considered. Its classified as a level 4 pathogen, so only few laboratories are qualified to culture the virus. Other rapid tests that can easily be performed with proper precautions include, antibody-captured enzyme-linked immunoabsorbent assay (ELISA), antigen detection tests (antigen-catch ELISA), serum neutralization test.

The patient's blood or serum is extremely infective, so care and precautions must be adequate. Because seroconvertion is between day 8 and 12, antigen detection should be the test of choice during the acute stage. IgM detection is appropriate during the convalescent period. IgG does not play any role in the diagnosis of EVD (9)

Preliminary tests such as a full blood count will indicate thrombocytopenia and leucopenia. Liver function test will also show elevated transaminases, and particularly when aspartate transaminases are more elevated than alanine transaminases, and when combined with the stated full blood count anomalies above, then filovirus infection should be suspected (4, 7, 9).

TREATMENT

There are few drugs and vaccines under development and, in fact, some are awaiting clinical trials. There is no specific treatment available yet for EVD; and no vaccine is licensed yet for human use.Treatment is basically those of intensive supportive care and proper hydration. Attention must be focused on correcting electrolyte imbalance. Replacement of coagulation factors and platelets may be necessary.

When clinical or laboratory evidence suggests intravascular coagulation, then heparin or other treatment forms for DIC may be necessary (7).

PREVENTION

African fruit bats of three genera are considered the natural habitat of Ebola virus. Fruit bats of the genera *Hypsignathus monstosus, Epomops franqueti, and Myonycte ristorquata* are thought to be the natural hosts for the virus. However, primates have been the main source of the infection to man. Several outbreaks have been seen in Gorillas and Chimpanzees (7). Therefore, reducing human contacts, particularly consumption of these animals is imperative for Africans to control animal-to-man transmission, which is often the primary source of epidemics. It is extremely important for people not to touch or play around such animals that are found dead or sick without a known cause.

During outbreaks, public education to raise awareness and increase knowledge should be the primary focus of public health practitioners and the government. Protective measures that individuals can take must be emphasized and information should be disseminated very efficiently and rapidly. In Africa, where outbreaks are common, the goal of public education and awareness should include the following; reducing the risks of animal-to-human transmission, reducing the risk of human-to-human transmission, and community affected need to be informed on methods to abort the spread of the disease.

Healthcare workers should always use standard precautions since they do not know when a new case will arise. There is no season for Ebola outbreaks, so standard precautions should be practiced at all times. Those caring for patients with suspected or confirmed cases should use ultimate infection control measures to ensure complete absence of exposure to blood or body fluids. Sterile gloves, face masks, long sleeve coats, protective shoes and goggles should be available to those who make close contacts with the patient. Trained laboratory workers in suitable (category 4 biohazard) laboratories should handle clinical specimens (7)

The role of platelets and cytotoxic T-lymphocytes from patients who have recovered from the disease in the passive immunization of patients and people who have been exposed to patients should be further explored. Lastly, the value of pooled serum of survivors in patients' management should also be explored further.

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