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EBOLA VIRUS DISEASE — PATHOGENESIS, CLINICAL PRESENTATION AND MANAGEMENT

Abstract: On March 2014 the WHO notified the outbreak of Ebola virus disease (EVD) in Guinea, and infection quickly spread to another West African countries including Sierra Leone, Liberia and Nigeria. Current outbreak is the largest in the history, since discovery of the virus in 1976. Imported cases and infection among healthcare workers in Europe and United States have elucidated necessity of better education of medical staff. Clinicians must be familiar with clinical picture of EVD, differential diagnosis and therapeutic approach, as rapid diagnosis and prompt introduction of supportive therapy can have a significant impact on the survival.

Key words: Ebola virus disease, pathogenesis, clinical presentation, diagnosis, treatment.

INTRODUCTION

Current outbreak of Ebola virus (EBOV) in West Africa can be described as most severe public health emergency in modern times [1]. The number of potential cases ranges from thousands to millions with mortality rate up to 74% [2]. The initial source of the outbreak appears to be a tiny village called Meliandou in southern Guinea where an index-case, a two-year old boy name Emille developed a haemorrhagic fever and died on 6th December 2013 [3]. On March 23, 2014, the World Health Organization (WHO) notified of an outbreak of EVD in Guinea [4]. Soon after that, the infection spread to Liberia and Sierra Leone. Imported cases have occured in Nigeria, but also in European countries and USA. An unrelated outbreak has been reported in Democratic Republic of Congo [4]. Infection among healthcare workers in developed countries has showed that we are not properly prepare for care of patients with highly communicable diseases, and continuous education including clinical picture and therapy of EVD but also methods of isolation and use of personal protective equipment (PPE) is essential for safety of healthcare workers, as well as prevention of further spread of this danger infection [1].

VIROLOGY

EBOV is zoonotic filovirus, comprised of envelope, nonsegmented negative-stranded RNA. Up to now five species have been identified: *Zaire ebolavirus*, *Bundibugyo ebolavirus*, *Tai Forest ebolavirus* (formerly known as Cote d'Ivore), *Sudan ebolavirus*, and *Reston ebolavirus* (found in Western Pacific, highly pathogenic in nonhuman primates) [5, 6]. Current West African outbreak, which is the biggest since the virus was discovered in 1976, is caused by Zaire ebolavirus [4].

Animal reservoir of the EBOV is considered to be the fruit bat. Transmission to humans required the contact with animal tissues or body fluids, including handling and ingestion of animal tissues, or ingestion of plants or water contaminated with bats faces or bodily fluids [7].

Occurrence of outbreak is related to human-to-human transmission. EBOV is usually transmitted through direct mucous membrane or percutaneous exposure to infected body fluids [7]. Most infectious body fluids are blood, stool and vomits. Virus also have been found in breast milk, urine and semen, but because can be detected up to 70 days these body fluids are considered to be less contagious. There is no enough evidence that saliva and tears are contagious, and the available data are conflicted. According the WHO there is no virus in the sweat. EBOV can survive on the solid surface up to 6 days, so the contact with them can potentially cause infection [5, 7–9].

PATHOGENESIS

After the infection virus is disseminated within the monocytes, macrophages, dendritic cells to the lymph nodes, and then by blood to the spleen and liver [7, 10]. EBOV entry, which includes attachment and penetration into the cytoplasm, is mediated by the surface glycoprotein (GP) [6]. This GP is a trimeric transmembrane surface protein that is critical for viral attachment to the host cells, and could be involved at many different levels in the EBOV pathogenesis [7, 11]. GP serve as a decoy antigen, be involved in antigenic subversion, and play a role in restoring the barrier function of endothelial cells. It is suggested that GP is involved in neutrophils inactivation and induction of apoptosis in bystander cells [11]. EBOV tropism toward antigen presenting cells (APCs) seems play also an important role in viral pathogenesis [12]. The infected APCs fail to undergo maturation; as such they are unable to present viral antigens to naive lymphocytes. This is followed by massive loss of uninfected lymphocytes due to the bystander effect of which lymphocytes undergo massive apoptosis due to the apoptotic induction of inflammatory mediators or loss of support signals from dendritic cells [7, 11, 12]. This result in complete collapse of adaptive immune response, including limited range of chemokines secreted by infected cells, failed expression of costimulatory

molecules, failed up regulation of major histocompatibility complex (MHC), inability of induced differentiation of allogenic lymphocytes [5, 7, 13]. Inhibition of interferon production is observed as well [7]. It was proved that patients who are able to develop antibodies within the second week of infection have cleared viremia and improved clinical symptoms. Once EBOV disseminates through the body, release of proinflammtory mediators and endothelial infection and dysfunction is observed. Progression of the disease is leading to the vasodilatation and increased vascular permeability, induction of extrinsic coagulation cascade and lymphocytes apoptosis [5, 7, 13]. Rasmussen et al. suggests that genetic factors play a significant role in determining disease outcome in naive individuals without prior exposure or immunologic priming [14].

CLINICAL PRESENTATION

Incubation period for EVD is 2 to 21 days (median 2 weeks). In current outbreak patients with EVD presented to the hospital 3 to 7 days (median 5 days) after the onset of symptoms [5, 15, 16].

Clinical presentation of EVD is very uncharacteristic and can mimic a lot of tropical diseases such as malaria, typhoid fever, cholera or Lasse fever, so to establish diagnosis the epidemiological data, must be strongly taken into consideration. As mentioned above EBOV is usually transmitted through direct mucous membrane or percutaneous exposure to infected body fluids, such as blood, stool, vomits, so during the history specific questions regarding the contact with any sick or died for Ebola individuals should be asked [5, 15, 16].

Initial symptoms, which usually begin abruptly, are non-specific symptoms of viral infections: fever, fatigue, headache, myalgia and malaise. Afterwards most patients are developing nausea, vomiting, anorexia, abdominal pain and diarrhoea. Lethargy, coughing, headache, hypotension are commonly observed. Haemorrhagic manifestations can vary in severity and are present in 30 to 70% of patients. These include maculopapular rash, mucosal haemorrhages, bleeding from the puncture sites, haemorrhages for gastrointestinal (GI) and genitourinary tract [5, 15, 16]. However, it should be stressed that in 2014 West African outbreak, number of cases with rash and other haemorrhagic complications were less frequent [19%], and primary clinical manifestation was gastrointestinal [2, 15]. In sever cases patients are developing hypovolemic shock and multiorgan failure, including hepatic damage, kidney and respiratory failure. Seizures and coma can occur as well [5, 15, 16]. Analysis of cases during the current outbreak revealed that most of the patients died 7 to 11 days after the onset of symptoms (median 8 days) [15]. In previous outbreaks mortality rate range from 30 to 90%. In 2014 in Guinea case fatality rate was 43% and in Sierra Leone 74% [2, 15].

LABORATORY ABNORMALITIES AND DIAGNOSTIC PROCEDURES

Laboratory findings include leukopenia, followed by leukocytosis and atypical lymphocytosis. Thrombocytopenia, as well as elevation of aminotransferases (AST and ALT) is a characteristic feature. Prolongation of the partial thromboplastin time and the international normalized ratio (INR) are common abnormality. As a consequence of vomiting and diarrhoea patients are developing electrolyte disturbances and later metabolic abnormalities [5, 7, 9, 10, 16].

To establish diagnosis viral RNA by PCR or viral antigen by immunoenzymatic methods (ELISA) should be detected in the blood or other body fluids. Rapid tests are available. It must be stressed that EBOV RNA can be detected 3 days after the infection, so in cases in which patient present to the doctor early and EVD is strongly suspected, the test should be repeated [5, 7, 9, 10, 16].

TREATMENT OF EBOLA VIRUS DISEASE

Currently, there is no specific treatment available for Ebola. There is also no therapeutics for prevention or post exposure. Several experimental therapies are under development, but not fully tested in human. However, FDA has approved some experimental treatments for emergency use in patients with Ebola infection [17].

One of them is brincidofovir — oral nucleotide analog, which is modified version of cidofovir. In vitro data suggest its activity against Ebola and recently FDA approved it for Phase 2 study [17].

The other antiviral drug — favipiravir, previously approved in Japan for treatment of flu, also showed promising results against Ebola in rodent model, but have to be confirmed in primates [18]. TKM Ebola and AVI 6002 are molecules used for blocking of viral replication genes via gene silencing. These drugs have shown effects against EVD in animal model but TKM Ebola's Phase 1 study was partially placed in a hold status by FDA, because of signs of cytokine release in patients treated with high doses of this drug [17]. ZMapp is another experimental treatment for EVD. It contains three monoclonal antibodies, which effectiveness against Ebola was proven in non-human primates. In experimental study, ZMapp was able to revert advanced EVD in primates when treatment was initiated up to 5 days after infection [19]. Unfortunately, all ZMapp supplies are exhausted at the moment. Another experimental therapy, already used during previous Ebola outbreaks, is passive immunization via convalescent whole blood and serum transfusion. However, the result of this method is controversial [1].

Without specific medications, treatment for Ebola is mostly limited to supportive care. Symptoms of EVD and its complications should be treated as they appear.

Hypovolemia due to massive fluid loss via vomiting, diarrhea and in rare cases vascular leak is the most common symptom of EVD. Clinical management should

focus on maintaining fluid volume and correction of electrolyte abnormalities. It's necessary to monitor daily fluid input and output, as well as heart rate and blood pressure. If tolerated, oral fluid replacement with rehydration solutions is preferred [16]. On the other hand, massive fluid loss needs more aggressive treatment and intravenous fluid therapy [1, 16]. It is preferred to use Ringer's solution than normal saline [20]. Because of increased risk of kidney failure, bleeding and mortality, colloids such as hydroxyethyl stach should be avoided [21, 22].

Severe electrolyte deficiencies, especially metabolic acidosis, hypokaliemia and hypocalcemia should also be expected. If the patient is able to eat, oral repletion of electrolytes is preferred [16]. However, massive electrolyte losses require intravenous replacement. Following management, when used early can improve chances of survival.

It was also observed that antiemetic and antidiarrheal drugs may limit massive loss of fluids via gastrointestinal tract and they should be considered [16].

Some patients may develop shock due to fluid loss, septic complications or bleeding. Shock is common manifestation of EVD severity and plausible lethal pathway [16]. This state require aggressive volume resuscitation and, when caused by severe blood loss, blood products transfusion. If needed, vasopressors such as dopamine or norepinefrine should be administered to maintain blood pressure.

If disseminated intravascular coagulation develops, replacement of coagulation factors, correction of thrombocytopenia and anemia is necessary [1].

Several patients with severe EVD may develop multiorgan failure. Acute kidney injury is one of the most common symptom of severe illness and it often needs renal replacement therapy. Liver failure, if occur, should be treated with supportive therapy [1]. It is also important to avoid possible nephrotoxic and hepatotoxic medications. On the other hand respiratory failure is more often secondary to other EVD complications than to primary respiratory insufficiency. In treatment non invasive oxygen therapy and mechanical ventilation in severe cases should be used [1].

Many patients with EVD may also have concomitant bacterial, viral or parasite infection [10]. If coinfection cannot be excluded, specific treatment is appropriate. Empiric treatment with antibiotics should be considered, especially at the beginning of the infection when the risk of bacterial translocation form inflamed intestine is high [16]. However, after excluding bacterial confection, antibiotics should be discontinued [16]. In African countries antimalarial agents should also be taken into consideration [1].

Other common symptoms of EVD like fever or pain should be treated with acetaminophen and opioids. NSAIDs, because of their effect on platelets should be avoided [16]. To minimalize hospital acquire complications such as stress ulceration or venous thrombo-embolic disease standard prophylactic should also be considered [1].

We cannot forget that most of the patients with EVD are unable to maintain oral intake due to nausea and vomiting and are in risk for malnutrition. In less severe cases antiemetic drugs, smaller volume of food and more frequent eating may increase tolerance for oral intake. Placement of nasogastric or orogastric tube may also be useful. In most severe cases, after 8 days of unsuccessful enteral nutrition, total parenteral nutrition is needed until adequate oral intake is possible [16, 23].

Giving that Ebola is highly contagious through direct contact with bodily fluids, contaminated objects and possibility of its aerosol route of infection isn't definitely excluded it is crucial to reduce the risk of human-to-human transmission. Isolation of the infected patients, protective cloths and equipment, control protocols, proper waste and samples management are essential to protect medical personnel and prevent spreading of the infection [1].

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