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Review Article

Ebola virus, a virus of mysterious origin: A review

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Abstract

Ebola virus is one of the causes of viral hemorrhagic fevers. Viral hemorrhagic fever is a severe disease that affects several organs. Ebola virus is one of the most dangerous viruses that causes severe disease in human and mammals. The transmission of this virus takes place through direct contact with the blood and body fluids of an infected person. Considering that usually, the first people who are exposed to this disease are healthcare workers, proper recognition and strict adherence to safety protocols are recommended when dealing with suspected patients.
The present study is a review-narrative research in which the articles indexed in the international scientific databases Science direct, PubMed, and Google scholar, limited to English and up to 2021, were used. After studying and evaluating the abstracts of 109 articles and removing irrelevant and repetitive studies, finally, 37 articles were reviewed and used.
The results of this review showed that the Ebola virus has the possibility of spreading in the world and causing widespread deaths; and requires strict control, the creation of a network for reporting suspicious cases, and more precise control of the country's borders for travelers from West Africa, in case of an outbreak. Despite numerous studies and recent advances, unfortunately, there is still no complete treatment and reliable preventive vaccine for Ebola virus. Doctors and nurses should know the travel or contact history of patients. Since the discovery of Ebola, 13 epidemics have occurred in Africa. In December 2013, a deadly epidemic occurred in West African countries, including Sierra Leone, Nigeria, Guinea, and Liberia. Cases of Ebola have been reported in the United States, Norway, Australia, and Spain. But this disease has not been reported in Iran. This study was conducted with the aim of providing new information about the Ebola virus and more awareness of the health care staff with epidemiology, pathogenic mechanisms, symptoms, diagnosis, advances in treatment candidates, and vaccines. Ebola virus is a zoonotic disease with high mortality. Ebola is fatal among animals and humans in Africa. Due to the fact that the natural history and reservoir of the Ebola virus have not been precisely determined and early diagnosis and identification of infection in humans and animals is very important, to prevent the spread of the disease, it is necessary to isolate and quarantine patients with fever and take precautionary measures.

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1. Introduction

Ebola virus is one of the most important and, at the same time, the most dangerous viral pathogens in humans. The epidemic in West African countries from 2013 to 2016 once again showed the importance of viral pathogens and the risk of their spread to different parts of the world to medical researchers, epidemiologists, vaccine and drug design specialists, and virologists.

Ebola and Marburg viruses belong to the Filoviridae family from the monongaviral order (negative sense single-stranded RNA), which were previously classified as part of the Rhabdoviridae

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family [1]. The Ebola virus genus has six species: Zaire, Sudan, Bundibugyo, Tay Jungle (Ivory Coast), Bombali, and Reston, but the Marburg genus has only one species, Lake Victoria Marburg [2].

The Marburg virus was identified in 1967 among laboratory staffs working with African green monkey tissues, and Ebola was first reported in a province of Sudan and an area near Zaire, where the Democratic Republic of the Congo is now located. These two viruses are antigenically different, but they cause a similar disease, and their reservoir hosts and carriers are unknown. The World Health Organization classifies these two viruses as pathogens of level 4 of biological safety due to high mortality, the power of person-to-person transmission, and the lack of antiviral drugs and vaccines [3]. There are still many unknowns about the Ebola virus. Various details regarding the epidemiology of the virus, its origin, and spread, mechanisms of pathogenesis, new methods of diagnosis and possible ways of treatment should be given more attention.

2. Methods

The present review-narrative study was conducted with the aim of more closely investigating these details and collecting information about the Ebola virus through searching and reviewing articles indexed in the international scientific databases PubMed, Science direct, and Google scholar limited to English language and prepared until 2021. The search in these databases was performed using the keywords "Hemorrhagic Fever, Ebola, Ebolavirus, Filoviridae Infections, Ebola Vaccines".

After studying and evaluating the abstracts of 109 articles and removing irrelevant and repetitive items, finally, 37 articles were reviewed and used. Finally, it is hoped that this article will make physicians and health care workers more familiar with this virus and the disease caused by it.

3. Results

3.1. Virion structure, genome organization, and virus proteins

Ebola virus is a member of the Filoviridae family. Under the electron microscope, it can be seen as a string (filament) and in cell culture as a polymorph (pleomorph). The length of this virus is 1400 nm, and the diameter is 80 nm (4). The genome of a single-stranded RNA virus with negative polarity and 18,959 base pairs long has the largest genome among menonogavirals and is one of the enveloped viruses [5]. The Ebola genome contains 7 genes, which include: 3'-NP, VP35, VP40, GP, VP30, VP24, and L-5' in order from 3' to 5'. In Ebola, on the one hand, there are inter-genomic regions that are non-coding regions, and on the other hand, there is an overlap between the sequences, which caused more different mRNAs to be produced, for example, the overlap between GP and vp30 caused the production of SGP. Perhaps one of the reasons for the production of different Ebola isolates is related to these gene overlaps. In such a way that the termination site at the 3' end of the upstream gene overlaps with the start site of the downstream gene. As a result, this overlap is limited only to the location of the transcription signal. The genome has a short extra-genomic sequence called the guide at the 3' end and a variable sequence called the trailer at the 5' end [6]. NP protein is the main nucleoprotein of the virus and is the first protein that is produced in the form of a gradient and has the role of protecting the genome, and is one of the capsid proteins [7, 8].

L and vp35 proteins form the polymerase complex, where vp35 acts as a cofactor and also a binding agent between L and NP. Also, like VP24, it is an antagonist of the INF-I pathway, thus preventing STAT from entering the nucleus [9, 10].

The main and sub-matrix of the virus are VP40 and VP24, respectively, which have the affinity to

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bind to the membrane. VP40 plays an important role in the virus's budding and the initiation of the nucleocapsid's coating through the plasma membrane in the process of virus replication [11, 12]. GP is the surface glycoprotein of the virus, which plays a role in the entry and pathogenicity of the virus and also acts as an antigen of the virus [13]. A non-structural glycoprotein called SGP has been identified in Ebola, which has the same amino acid as the amino end of GP, but differs from its carboxyl end. SGP is secreted from the cell as a homodimer after cutting with furin. This protein may be effective in the progression of the disease [6,14].

3.2. Virus replication and effects of replication on host cell culture

The virus binds to its receptors (which include C-type lectin, DC-SING, and integrin) through glycoprotein GP [15]. The acidic pH of the endosome and cellular enzymes cause the virus coat to be digested and the nucleocapsid to be released into the cytoplasm [16]. After entering the nucleocapsid into the cytoplasm,L enzyme transcribes monocistronic mRNAs with 5'cap and 3'polyA. By placing in the intergenomic regions and encapsulating antigenic RNAs, NP proteins change the direction from transcription to replication. When the genome and the capsule proteins are produced enough, a gathering of these components occurs in the plasma membrane in the lipid regions, and finally vp40 facilitates virus budding [17, 18]. Ebola causes cytopathic effects (CPE) in cell cultures and kidney cell lines of African green monkeys. Studies have shown that GP expression has cytotoxic effects for cells [6].

3.3. Pathogenesis

The infection is transmitted through direct contact with the blood and secretions of an infected person or animal. Then the virus enters the body through mucosal surfaces and skin scratches. Transmission through aerosols is also considered [19]. Interestingly, during the initial phase of the epidemic, which occurred in West Africa in 2014-2015, hundreds of nurses and doctors who were caring for infected patients were infected with the virus. This shows that healthcare workers are at high risk of infection, and washing Ebola victims has played an important role in the epidemic of infection and contributed to its epidemic in West Africa. The virus survives on surfaces for hours to days. There is no evidence to support its transmission through exposure to surfaces. But cleaning the environment reduces the risk of transmission [20]. Fruit bats can carry the virus without being infected [21].

The primary targets of the virus are macrophages and dendritic cells, which by inhibiting the induction of interferon, cause the virus to become systemic and finally go to the liver, spleen, thymus, and lymphoid tissues, where they multiply and cause tissue necrosis. Gastrointestinal complications caused by this virus, due to infection or stimulation of cytokine production, are diarrhea and vomiting, which lead to loss of body fluids, drop in blood pressure, and shock. Adrenocortical infection and necrosis of the adrenal cortex, due to the role of this organ in regulating blood pressure, causes incomplete secretion of steroid synthesizing enzyme and ultimately leads to a decrease in blood pressure, loss of sodium with hypovolemia, and finally causes shock in the last stage of the disease. Infected macrophages synthesize tissue factor, and pro-inflammatory cytokines, by acting on macrophages, increase this synthesis ; tissue factor itself causes disruption in the coagulation process [19, 22].

3.4 Epidemiology

Ebola was identified in Sudan and Zaire in 1976. The first Ebola, with a mortality rate of 53% is related to Sudan, and a few months later,

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the second Ebola, which was isolated in Zaire, showed the highest mortality rate (about 88%). Despite the efforts made, the reservoir of Ebola was not identified in that epidemic. The third Ebola (Ebola Reston) was detected in monkeys in the Reston area in 1989, but the number of infected people was very small; the fourth known strain of Ebola (Ivory Coast Ebola) was identified in a woman working on a chimpanzee corpse in 1994 in Ivory Coast [23]. Since the discovery of the virus, 21 epidemics have been reported in Africa. From 1976 to 2008, the mortality rate of Ebola was 79%. In December 2013, an epidemic began in West Africa (Guinea), and its mortality rate was 33% to 73%, then it reached Sierra Leone, Liberia ,and Nigeria, and in May 2014 it caused a second epidemic in these countries; the number of victims in the October of that year reached 4,555 people. This, along with another epidemic that occurred in Angola during 2000-2001, were the biggest epidemics in the history of Ebola [5, 24]. In addition to African countries, Ebola cases have also been reported in America, Norway, Spain, and Australia [25].

3.5 Clinical and laboratory findings

The incubation period of the disease widely daries depending on the type of Ebola and the way it enters the body. For example, the incubation period after transmission through the needle sticks in the Ebola species of Sudan lasts 6 days, but for Zaire, it lasts 7 days. In contact with chimpanzees, this incubation period lasts 8 days, and in transmission with bats, 13 days. After the incubation period of 3-21 days, the disease appears with flu-like symptoms, and then the fever reaches 38.3 degrees. Severe headache, muscle pain and chest pain, abdominal pain, joint pain, diarrhea, vomiting, conjunctival infection, decrease in blood pressure, liver and kidney dysfunction, and edema occur. Internal and external bleeding and petechiae (due to coagulation defects) are observed five to seven days after the first symptoms appear [25, 26]. Death occurs on days 6 to 16 due to blood pressure drop, fluid loss, and bleeding. The mortality rate in Zaire Ebola is about 60% to 90%, and in Sudan Ebola virus it reaches 50% to 60% (6, 27). Those who recover suffer from constant muscle and joint pain, liver inflammation, weakness, fatigue, loss of appetite, and hearing loss. These people cannot transmit the disease for a long time. The antibody against Ebola remains in the serum of these people for up to ten years, but it has not yet been determined whether these antibodies can completely protect a person against re-infection with Ebola or not [28].

Laboratory findings of infection depend on the effects of the virus on the target tissues. For example, with an indirect effect (production of pro-inflammatory cytokines IL1, IL6, and TNF) on the liver, it increases CRP production and decreases albumin production; and with a direct effect on the liver, it causes an increase in liver enzymes ALT, AST, ALP, and gamma globulin transferase(GGT).

Kidney function is also affected, which leads to increased blood urea and creatinine, oliguria, hemoglobinuria, and hematuria. With the disorders it creates in the coagulation system, it prolongs BT, PT, and PTT; and also causes disseminated intravascular coagulation (DIC) and an increase in D-Dimmer, which increase in D-Dimmer level is directly related to mortality rates [29, 30].

3.6 Diagnosis and treatment

Specific and initial diagnosis of Ebola includes virus isolation using cell culture, detection of Ebola RNA by RT-PCR method, and detection of virus proteins by ELISA method [31]. The most sensitive test that is performed today, is the ELISA test using recombinant NP antigen [27, 32]. Since the virus titer may be high and the virus is stable for a long time at room temperature, it is necessary

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to be careful in collecting and transporting blood samples; and for immunological tests, the samples must be deactivated by gamma radiation or 60 degrees temperature for 30 minutes. Also, level 4 biological safety conditions are necessary for virus isolation [6]. The detection of antiviral antibodies is the most reliable test in the later stages of infection and in those who have recovered. IgM, two days after the onset of symptoms, and IgG on days 6 to 18 can be detected in the blood [31]. The initial symptoms of Ebola are similar to malaria, dengue fever, Marburg, other hemorrhagic diseases, and even infectious diseases such as typhoid, shigella, rickettsia, and cholera. Also,the symptoms of non-infectious diseases such as acute promyelocytic leukemia, hemolytic uremic syndrome, Kawasaki disease, warfarin poisoning, deficiency of coagulation factors, and platelet disorder may be similar to the symptoms of patients who have EVD (Ebola virus disease). Therefore, differential diagnosis of the disease is very important [33]. No specific treatment or vaccine has been identified for Ebola disease so far, and mostly, conservative treatments are carried out, including providing water and electrolytes, taking anticoagulant drugs in the early stages of infection and preventing bleeding, using antibiotics and antifungal drugs, treatment of secondary infections, and control of oxygen level and blood pressure.

During the recent outbreak of the Ebola virus and its spread in the Democratic Republic of Congo, the monoclonal antibody mixture ZMapp from Mapp Biopharmaceutical Company, REGN-EB3 from Regeneron Pharmaceuticals Company, as well as the single monoclonal antibody Mab114 from Ridgeback Biotherapeutics Company, and finally remdesivir from Gilead Sciences Company , which is a drug with direct antiviral effect, has been used [34-37].

It is noteworthy that patients who received treatment earlier, compared to those who were in the advanced stages of the disease, have responded better to treatments, and therefore, quick diagnosis and immediate treatment can play an important role in helping patients [38]. The Inmazeb or REGN-EB3, which consists of three human monoclonal antibodies Atoltivimab, Maftivimab, and Odesivimab, showed significant positive results for the treatment of Zaire ebolavirus infection in adults and children in the PALM clinical trial [39, 40].

4. Discussion

Researchers still do not know why some infected people with this virus recover and others die, but some patients who die do not have a strong immune response. Since the natural progression of the disease and the reservoirs of the virus are not known properly, and there is no specific method to avoid infection, it is vital to quickly diagnose and identify the infection in humans and animals. Due to the fact that the rapid transmission of Ebola and its subsequent epidemic causes a lot of economic and human damage, therefore, the prevention of this disease plays the most important role in compensating for the damages. Identifying the source of the virus in Africa faces many difficulties because the identity and habitat of the animals that are the reservoir of Ebola is unknown. However, if cases of this disease are observed, the first ones who should be very careful are health care workers. These people should use full cover, mask, gloves, and glasses when dealing with suspected cases of this disease. The purpose of this necessary precaution is to prevent contamination with the blood and body secretions of the infected person. Also, if the patient dies, contact with the body should be avoided.

5. Conclusion

The most important thing to do in the process of controlling the spread of the infection is to set up a special monitoring system for this disease in endemic countries and regions where even one

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case of Ebola has been reported.

Isolating patients with fever and quarantining infected patients, as well as performing strengthening treatments such as helping to maintain the patient's blood pressure, maintaining body fluids, and helping the patient to breathe are considered essential measures.

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Conflict of interests

The authors have no conflicts of interest with individuals or organizations.

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