CLINICAL PRACTICE

Re-emerging infectious diseases: Ebola hemorrhagic fever

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Abstract: *The spring of 2014 has brought a new calamity, the exotic infectious disease: Ebola Hemorrhagic Fever, which is caused by a highly contagious and pathogenic virus, transmitted directly by interpersonal contact or indirectly by common usage of objects. The epidemic which occurred in Guinea tended to expand to neighboring countries; 83 deaths have been reported on April 1st 2014. Genetic analysis have revealed that the virus that causes this epidemic is similar in a proportion of 98% to Ebolavirus Zaire (EBOV) species that were responsible for the epidemic in Democratic Republic of Congo, in 2008.*

The Ebola virus belongs to the Filoviridae family, Ebolavirus genus and causes Ebola Hemorrhagic Fever, with a rate of fatality of up to 90% in humans. There are five distinct species: Bundibugyo Ebolavirus (BDBV), Ebolavirus Zaire (EBOV), Reston Ebolavirus (RESTV), Sudan Ebolavirus (SUDV) and Taï Forest Ebolavirus (TAFV).

Keywords: *Ebola, Hemorrhagic Fever, exotic diseases, epidemic*

INTRODUCTION

The spring of 2014 has brought a new calamity, an exotic infectious disease – Ebola Hemorrhagic Fever, which is caused by a highly pathogenic and virulent virus, highly contagious by interpersonal contact or through objects. Epidemic which first occurred in Guinea tended to expand to neighboring countries and beyond, on April 1st 2014, 83 deaths cases being reported. Genetic tests have revealed that the virus that causes this epidemic is similar in a proportion of 98% with Ebolavirus Zaire (EBOV) species, which were responsible for the epidemic in the Democratic Republic of Congo in 2008.

Ebola virus belongs to the Filoviridae family, Ebolavirus genus and causes Ebola Hemorrhagic Fever, a fatal disease to humans in more than 90% of cases. Five distrinct species have been identified: Bundibugyo Ebolavirus (BDBV) Ebolavirus Zaire (EBOV), Reston Ebolavirus (RESTV), Sudan Ebolavirus (SUDV), Tai Forest Ebolavirus (TAFV) by now (http://ecdc.europa.eu).
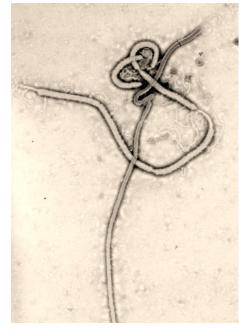
The virions have the characteristic appearance of rod or filaments in the form of U or 6, or entangled branched. Type of genome is RNA (ribonucleic acid) linear, single-stranded, negative-sense (1) (Figure 1).

Ebola Hemorrhagic Fever is an acute viral infection characterized by an incubation period of about 8 days, with extremes of 2-21 days. Onset occurs suddenly, with high fever, chills, headache, myalgia, anorexia associated with rash. In the next 2-3 days appear nausea, vomiting, pharyngitis and hemorrhagic phenomena, haematemesis, melaena, bruising and petechiae. Nervous disorders appear, accompanied by prostration, anxiety, confusion, and

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memory loss and balance disorders. Laboratory analyses show a low number of leukocytes and platelets and an elevated liver enzymes. Abortion in pregnant women occurs in 66% of cases and newborns of infected mothers fatally infected. Mortality in pregnant women is 95.5%.

Figure 1. Virus Ebola – electronic microscope image (Centers for Disease Control and Prevention, USA)

Death may occur, in 6-9 days after the illness debut, by hemorrhagic shock with massive and generalized bleedings. Virus and viral antigen are present at high levels in the blood and organs. In case of illness remission, convalescence is long and is accompanied by intensive hair fall for about 3 month, extreme fatigue, anorexia, abdominal pain, myalgia and arthralgia, hearing loss in 6 months after acute phase.

Myalgias and arthropathies are described even after 21 months. Infected people are contagious as long as their blood and secretions contain the virus which could be isolated from semen until day 61 after debut and persists for patients in recovering.

Viral RNA was revealed in vaginal, rectal and conjunctival samplings after 33 days, and presence of viral RNA in semen was demonstrated for 61, 82 and 91 days after illness onset (1).

EPIDEMIOLOGY

History. The Ebola virus was first identified in 1976 during the epidemic in Zaire (Democratic Republic of Congo) and Sudan. Natural infection cases were reported in Africa: Democratic Republic of Congo (1976, 1977, 1995, 2007, 2008, 2012), Sudan (1976, 1979, 2004), Gabon (1994, 1996, 2001, 2002), Ivory Coast (1994), Uganda (2000, 2001, 2007, 2011, 2012), Congo Republic (2001-2003, 2005), Guinea and Liberia (2014). In England (1976) was reported an accidental infection in a laboratory. Ebola was introduced into quarantine facilities in the USA (1989, 1990, 1996), in Italy (1992) and the Philippines (1996) (www.who.int, www.ecdc.europa.eu).

Ebola in Uganda/2012

On July 29, 2012 Ministry of Health of Uganda has notified the World Health Organisation (WHO) on an outbreak of hemorrhagic fever in a western area of the country, Kibaale, with 20 cases and 14 deaths. Since the beginning of the epidemic was reported a total of 24 human cases (confirmed or probable) and 17 deaths. Laboratory tests conducted by Uganda Virus Research Institute (UVRI) and Centres for Disease Control and Prevention (CDC) confirmed the presence of Ebola Sudan virus in 5 patients, from which 2 died. All reported infection cases and infected people contacts were investigated (www.cdc.gov). On October 4, 2012 Ministry of Health of Uganda said that the epidemic ended.

Ebola in Democratic Republic of Congo/2012

On August 17 2012, Ministry of Health of Democratic Republic of Congo reported an outbreak of Ebola hemorrhagic fever with 10 suspected cases and 6 deaths. Laboratory tests conducted by Uganda Virus Research Institute (UVRI) and Centres for Disease Control and Prevention (CDC) confirmed the presence of Bundibugyo Ebola virus in 2 patients. However, epidemic in the Democratic Republic of Congo it is not epidemiologically linked to the one in Uganda. Final Report of November 26 shows a total of 77 cases of which 36 were confirmed by laboratory tests, 17 were probable, 24 were suspicious and 36 deaths were reported (www.cdc.gov).

Ebola in Guinea and Liberia/2014

On March 22, 2014, the Ministry of Health of Guinea notified WHO about an outbreak of Ebola Hemorrhagic Fever in the forested southeast areas, rapidly evolving, with a total of 49 cases, including 29 deaths (fatality rate: 59%). On March 30, 2014 a total number of 112 suspected cases of Ebola virus infection were reported, from which 70 were deaths and on April 12; Centres for Disease Control announced 83 deaths; 35 of these cases were confirmed by laboratory tests carried out in several laboratories, including Pasteur Institute, Lyon in France, Institute Pasteur, Dakar in Senegal and Bernhard Nocht Institute for Tropical Medicine, Hamburg in Germany, using PCR (Polymerase Chain Reaction).

Liberia has reported 8 suspect cases, including 5 deaths, and two laboratory confirmed cases in people who recently travelled in Guinea. Ministry of Health of Guinea and WHO have implemented measures to control the spread of the epidemic and to restrict travels and trade till the problem is solved (www.cdc.gov).

The natural infection

Source of the virus still remains unknown, but it is suspected that virulent strains used as hosts could be species which come less in contact with people. The transmission is achieved by direct contact with sick animals or humans through blood, organs, secretions or excretions or by sexual contact. Contamination by aerosols (6), although it is not regarded as the main route of transmission, has been incriminated in the 1989 epizootic in Reston (the virus was isolated from monkeys).

The nosocomial transmission (by linen, syringes, needles and other contaminated material) should be considered to impose preventive measures. The susceptibility related to natural infection is generalized and the resistance to infection or re-infection is not known (1).

Biological weapon

The Ebola virus is a potential biological agent to be used in bioterrorism because it causes a highly severe disease and the means of defence against this virus are extremely poor for the moment. Russian researchers have shown that low doses of Ebola virus administered by aerosols could cause infections in monkeys, implying mortality.

There is no effective therapy for infection prevention, nor vaccines are available so this virus may be considered as a potential bio-terrorist biological agent (4). We should not forget that at the first outbreak of Ebola in Africa, among the international volunteers, representatives of the AUM sect from Japan also came whose they real target was to take with them virus strain samples, possible in intention to cause biological attacks. Fortunately, Interpol has prevented on time that fact, counteracting in an antiterrorist manner. There are suspicions that some armies would have developed an Ebola-Smallpox hybrid virus as a biological agent, hybrid which would benefit from a maximum of pathogenicity, virulence and infectiousness and for which there is no effective treatment.

LABORATORY DIAGNOSIS

Necessary samples for analysis in the acute fever stage are: serum, heparinied plasma, nasopharyngeal washings, urine, soft tissues blood samples, skin biopsies.

Necessary samples for analysis in the recovering stage are: semen, eye discharge.

Necessary samples for postmortem analysis are: fragments of organs (spleen, lymphatic nodes, liver, and kidneys).

After sampling, the pathological materials are going to be maintained in triple layered packaging, according to WHO recommendations (perfect sealed plastic bags with clear inscriptions, in resistant containers, protected against leakage).

These containers are to be proofed against outside surface contamination. Samples will be stored frozen in liquid nitrogen or dry ice. Due to the high contamination hazard, handling of infectious materials will be made with special precautions in laboratories that have an appropriate grade of bio-

safety, level 4, regarding personnel and technical equipment (1).

According to CDC recommendations, the virological diagnosis is presented in Table 1.

In Romania, suspicious samples could be analyzed for laboratory diagnosis at the National Institute of Research and Development for Microbiology-Immunology Cantacuzino (NIRDMI Cantacuzino) and the Institute of Virology "Stefan Nicolau" in Bucharest, but there are no facilities BSL4 (Bio-safety Level 4 Laboratory highly security).

In veterinarian medicine, the sample analysis may be performed at Institute for Diagnosis and Animal Health Bucharest (IDAH), where two laboratories BSL3 are functional. In Medical Center of Military Scientific Research in Bucharest (MCMSR) there is a highly secure microbiological laboratory, but is still under construction.

Table 1. Laboratory diagnosis schema for Ebola, according CDC

Timeline of Infection	Diagnostic tests available
Within a few days after symptoms begin	Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing IgM ELISA Polymerase chain reaction (PCR) Virus isolation
Later in disease course or after recovery	IgM and IgG antibodies
Retrospectively in deceased patients	Immunohistochemistry testing PCR Virus isolation

TREATMENT

The European Medicines Agency confirms that there is no specific treatment for Ebola Hemorrhagic Fever (www.ema.europa.eu). When cases of infection with Ebola virus occur, the sole treatment is the supportive one.

Patients are usually dehydrated and, therefore, require administration of fluids intravenous or oral with solutions that are composed of electrolytes (www.who.int).

Effective antiviral compounds do not exist yet and ribavirin has no effect on the Ebola virus. Administration of interferon has neither given satisfactory results nor in experimental treatments of disease neither in monkeys nor in patients.

Some promising results were obtained when 3-deazadenosine carbo-cyclic was used to treat experimental infection with lethal doses of Ebola virus in mice: survival rates up to 90% when treatment was started after 2 days from the infestation, and 40% after 3 days (1) .

PROPHILAXY

Since there is no clear data on the reservoir of infection, we are not able to speak about a classical approach for infections control. It may take measures of putting animals under quarantine at most, and in case of death of those animals or illness of carers, with fever over 38.5°C for a period longer than two days, it could be considered as a suspected Ebola virus infection and, accordingly, action would be taken.

Patients will be kept in strict isolation, possibly with bed isolation devices. All materials, objects, tools etc. which came in contact with the patient should be transported in a separate facility and sterilized. Health care personnel will be equipped with protective clothing (possibly sealed, with positive pressure), masks, gloves, shoes. It is desirable to prevent contamination by the aerosol, the air is recommended to be filtered through HEPA type filters (1). Patients' transportation is recommended to be made by sealed stretchers equipped with filtered ventilation system (www.karcher-futuretech.com), like that one presented in Figure 2.

Figure 2. Transportation system provided with patient decontamination facility (www.karcher-futuretech.com)

Vaccination

No approved vaccine is currently against Ebola virus currently available on market. However, laboratory tests are promising and their results are being evaluated (www.who.int). For example, a team of researchers from Arizona, is studying a vaccine that protects mice against infection with Ebola virus.

This vaccine includes a surface glycoprotein of the virus, combined with a monoclonal antibody and a chemical substance which activates biochemical cascade involved in natural immunity. More than 80% of the mice receiving this treatment, survived after administration of high doses of Ebola virus (5).

RNA experimental therapy has revealed satisfactory results in experiments on monkeys, researchers at Boston University School of Medicine suggesting that this therapy could induce protection in humans, providing hope for the future (3).

COMMENTS

According with World Health Organisation, the last Ebola Situation Report, from 11 February 2015 presents the following: "There have been almost 23 000 reported confirmed, probable, and suspected cases of EVD in Guinea, Liberia and Sierra Leone, with almost 9000 reported deaths (outcomes for many cases are unknown).

A total of 65 new confirmed cases were reported in Guinea, 3 in Liberia, and 76 in Sierra Leone in the 7 days to 8 February.

Six countries (Mali, Nigeria, Senegal, Spain, the United Kingdom and the United States of America) have reported a case or cases imported from a country with widespread and intense transmission.

The introduction of a case into unaffected countries remains a risk for as long as cases are reported in any country. With adequate levels of preparation, however, such introductions of the disease can be contained with a rapid and adequate response.

The response to the EVD epidemic has now moved to a second phase, as the focus shifts from slowing transmission to ending the epidemic. To achieve this goal as quickly as possible, efforts have moved from rapidly building infrastructure to ensuring that capacity for case finding, case management, safe burials, and community engagement is used as effectively as possible."

CONCLUSIONS

Origin and virus reservoir remain unknown and have to be pursued by:
- development of new systems for early diagnosis of Ebola virus infection, which could help epidemiological investigations;
- monitoring of suspicious areas in order to determine the incidence of the disease;
- acquiring extensive knowledge on natural virus reservoir and mode of transmission, which could be useful in preventing epidemics.

Epidemics in Uganda and the Democratic Republic of Congo have been monitored by the World Health Organization (WHO) and were limited.

Currently, they are trying to limit the epidemic in Guinea, which is under observation WHO.

It is necessary to establish anti-epidemic measures in relation to the affected countries to prevent a possible import of Ebola virus. It is highly recommended to avoid travelling to epidemic areas.

Furthermore, this epidemic should be a lesson -

learned for the upcoming epidemics.

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