Chapter

The Emerging Challenges in Transmission and Detection of Filovirus Infections in Developing Countries

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Abstract

This chapter reviews the emerging challenges in the transmission and detection of Ebola and Marburg filoviruses since their identification in 1967 and 1976, respectively. Five known highly fatal Ebola species are examined. Ebola outbreaks comprising of 14 EBOV, 7 SUDV, and 4 BDBV infections are reviewed, including the largest West African Ebola outbreak. The ecology of filoviruses and the possible interactions with intermediate hosts and reservoirs is also examined. Evidence that bats are the principal reservoirs of these infections is reviewed. Surveys raise the possibility that other nonhuman primates including dogs may be involved. Challenges on the presumed modes of transmission are discussed with a possibility of droplet and aerosol routes. The discovery of Ebola virus in pigs and its potential impact on the food chain are discussed. The WHO Syndrome Case definition guidelines for diagnosis are examined and shortcomings discussed. However, the early case detection is undermined by the many tropical diseases with similar symptoms. The low positive predictive value for diagnosis based on the antibody antigen assays in outbreaks complicates early isolation and action especially in resource constrained settings. The chapter suggests improvements and areas for further research on the ecology, transmission, and management of filovirus infections.

Keywords: filoviruses, Ebola, Marburg, ecology, reservoirs, transmission, detection

1. Introduction

The filovirus infections are emerging new infections, which pose serious public health threats of global dimensions. This filovirus family comprises mainly of the Ebola virus and the Marburg virus. Some five species of Ebola have been confirmed and includes the Zaire Ebola virus (EBOV), the Sudan subtype (SUDV), the Bundibugyo virus (BDBV), the Tai Forest virus (TAFV), and the Reston virus (RESTV) [1, 2]. Most of the outbreaks have been caused by EBOV and SUDV infections. The TAFV has caused single causality. RESTV is associated with asymptomatic infection among nonhuman primates and pigs [3]. There is yet no known bat hosts for the Sudan, Bundibugyo, or the Tai Forest Ebolavirus.

The Marburg virus was first isolated in 1967 when laboratory workers in Marburg, Germany and Yugoslavia were infected when exposed to imported green monkeys from Uganda [4, 5]. Between 1975 and 1997, a few sporadic cases of Marburgvirus (Marburg virus and the Ravn virus) were reported in South Africa. This was followed in 1980 and in 1987 by sporadic cases in Kenya [1, 4]. Between 1995 and 1999, small outbreaks of Marburg were reported in the Democratic Republic of the Congo. Larger Marburg outbreaks have occurred in the Republic of Congo (1998–2000), Angola (2004–2005), and Uganda (2007–2008) [6, 7]. In 2012, four more similar outbreaks were reported in Uganda and the Democratic Republic of Congo.

The Ebola virus was first identified in 1976 in a major outbreak in 1976. The disease was located in Kikwit near Ebola river in the then northern Zaire [8]. At the same time, a similar outbreak caused by the Sudan subtype also occurred in the current Southern Sudan. Both infections resulted in a high case fatality rate (range 53–89%). Clinical features include high fever, hemorrhagic manifestations, and coagulation defects. Minor outbreaks followed occurring in the Eastern (formerly) Zaire in 1977. Some 34 cases also occurred in Sudan in 1979. There were no further Ebola outbreaks until 1994. From 1994 to 1997, there were a number of outbreaks in DRC, to be followed subsequently by several epidemics between 2000 and 2004 [9]. In 2000, a large outbreak occurred in Gulu Uganda during which 224 cases and 173 deaths were confirmed [10]. In 2007, a novel Bundibugyo Ebola virus caused 116 cases and 39 deaths in Western Uganda [7]. During the same year, a similar outbreak occurred in DRC involving 260 cases with 186 deaths. In several instances, the index case was linked to eating of bats as food [11, 12]. In 2012, three minor outbreaks occurred in Uganda; and one more was reported in the Democratic Republic of the Congo. From 2013 to 2015, the largest Ebola outbreak occurred in West Africa (Guinea, Sierra Leone, and Liberia). It resulted in 28,652 cases and 15,261 deaths affecting heavily the healthcare workers [14]. In May 2018, a new Ebola outbreak erupted in the Equateur Province of the Democratic Republic of the Congo and 50 cases and 25 deaths were reported [13]. In 2019, there is a current ongoing serious outbreak of Ebola in the Eastern Democratic Republic of the Congo on the border with Uganda and over 1000 deaths have so far been reported by September. A single imported case was reported in Western Uganda but was quickly contained. Since 1976, some 25 Ebola outbreaks were reported and comprised of 14 EBOV outbreaks, seven more due to SUDV, and four linked to BDBV infection. In Uganda, some five Ebola outbreaks have been confirmed [15], major one in 2000 and four in 2012.

The aim of this chapter is to review the current knowledge on filoviruses as emerging infections based on published literature with a focus on Ebola and Marburg virus infections and outbreaks. The chapter examines the challenges related to their ecology, transmission, and detection, particularly in developing countries.

2. Role of bats

The natural history of filoviruses remains rudimentary and largely not well understood. The perceived view is that their transmission is a zoonosis linked to wild life, particularly bats. Bats have an economic and ecologic impact on the environment in several ways depending on their feeding habits as insectivorous, frugivorous, or nectarivorous. Bats facilitate plant pollination and the control of insects. Bats are also often eaten in parts of Africa. Falling fruits are often a shared food resource with nonhuman primates and other animals. During the West

African Ebola outbreak, serologic evidence also showed that 31.8% of the dogs were infected, but Ebola like symptoms were not detected in dogs [14]. Studies suggest that nonhuman primates are equally susceptible. An Ebola outbreak occurred among a chimpanzee community in the Tai National Park in Ivory Coast [16] suggesting that they may not be reservoirs. Similar epizootics among other wildlife have also been documented in Gabon [17]. It is possible that Marburg and Ebola persist in hosts that are rare. Recently, a new Ebolavirus called Bombali virus (BOMV) was isolated in house dwelling bats in Sierra Leone raising the possibility of other transmitters [18]. The persistence and resilience of bats and association with most such epidemics remain elusive.

Nonetheless, bats have been recognized as the reservoirs of Ebola. When experimentally inoculated with the Ebola virus, the bats got infected but survived [19]. Surveys have also detected anti-Ebola IgG antibodies in bats [11]. The 2007 outbreak of Marburg virus disease in Kamwenge district in Uganda was associated with a large colony of bats in Kitaka mine. A survey of bats in the cave revealed that 5% of the thousands of fruit bats in the mine were harboring the Marburg virus [20]. The presence of Ebola and Marburg virus antibodies in fruit bats [9] has also been confirmed. Antibodies against ZEBOV and RESTV have also been detected from bats in Indonesia, China, and Bangladesh [21, 22]. Transmission risks could be increased during mating, birthing, or in group migration. These events are seasonal. Understanding their ecology and habits provides critical knowledge on perceived risks associated with seasonality. Indeed some studies have revealed that high transmission is associated with birthing [23].

Studies on cross immunity and reactivity amidst circulating filovirus antibodies in bats could evaluate the extent of their asymptomatic status. Studies should be done to determine the routes of infection and to assess the viral load in tissues of bats and related sources of infection. Little is known about the natural long term immunological, pathological, and clinical responses to filovirus infection in bats. Studies on immunological responses in bats in their natural settings are required to determine the role of bats in harboring and sustaining infection. The apparent observed asymptomatic infection despite the viremia and apparent immunity in bats needs long-term investigation. There are still gaps in identifying routes of viral shedding, seasonality, other animal and probably insect reservoirs in the ecology of these viruses. The observed relationships and potential implications need further exploration of the ecology of the filoviruses in their natural hosts.

The geographical range of bats able to be hosts filoviruses is reported to be very extensive and geographically very broad. For instance, bats in the Iberian Peninsula were reported to have died of viral pneumonia in a cave in Northern Spain (Cueva del Lloviu). The cause was reported to be due to a new filovirus named Lloviu virus [24]. There are over 1200 species of bats identified globally, of which only a few have been screened for filoviruses [21].

3. Challenges in transmission

Epidemiological evidence suggests that the major mode of transmission for Ebola and Marburg infections is through direct contact with infected blood or body fluids. Nonsterile needles and administration of blood equally pose a potential risks especially in low resource settings. Thus, healthcare workers and bed side healthcare givers of patients are exposed to exceptional nosocomial risks [7, 25, 26]. Long-term persistence of Ebola in semen (up to 179 days) has been shown post recovery. There

are also reports of Ebola transmission occurring through breast milk of asymptomatic individuals during the West Africa outbreak. These observations underscore the possible transmission through breast feeding and sexual contact with survivors of infection [27, 28]. Large scale outbreaks of Marburg virus have been linked to mines and caves [6, 20, 29] suggesting the possibility of other routes of spread. In such circumstances, it is not clear whether the routes of infection are via droplets, bat excreta, or even the aerosol route. Aerosols are generated from the respiratory tract through coughing, breathing, and talking and could cause droplet or airborne spread of infection. This could be a rare but important mode of spread of infection. However, data on this concept are small and the role of aerosol route emerging as a possibility needs to be examined. In addition, the role of fomites in amplifying transmission and spread of the infection needs investigation. Additional studies are required to segregate the significance of aerosol and droplet transmission. Ebola virus has been isolated from saliva and pulmonary alveoli in experimental animals; thus, making a case for the droplet transmission. Cough and pneumonitis is a symptom of both Ebola and Marburg filovirus disease and further strengthens the infection potential via this route as already demonstrated and suggested by RESTV experiments with pigs and monkeys. However, it is possible that some patients infected with the EBOV West African Strain (Makoma) have higher viral loads and infectivity [14]. Further studies are required to determine the dynamics and mechanisms for such transmission through indirect contact. There are also reports that pigs when infected with Ebola virus can infect the cynomolgus macaques in the absence of direct contact. Animal to animal studies have also demonstrated fatal infection through inhalation of aerosol and droplets in caged monkeys. Similar other animal studies have demonstrated the transmission of Ebola like disease in inoculated monkeys [30].

Nonetheless, isolation of patients remains the basis for containing the further spread of infection [31]. However, this has not always been perfect in low resource settings. In Uganda, it has been reported that 64% of the 31 infected healthcare workers got infection after the provision of personal protection measures and the establishment of isolation facilities [15]. The inadequacy of training on use of personal protection material was postulated as a contributing factor. False assurance and complacency that the general wards were safe could have compromised protection. Other victims included support staff like ambulance drivers felt a false sense of security since they were not working in the isolation wards. Some of the victims worked exclusively in general wards or were support staff like ambulance drivers and cleaners. However, there may be other host factors including societal obstacles such as special attachment when caring for dear relatives, which accentuated vulnerability to infection.

4. Challenges in clinical detection

Early detection remains vital for prompt action for the control of filoviruses in emergencies. Clinical assessment based on symptoms assisted by the laboratory is usually applied to identify and manage cases of Ebola of Marburg Virus diseases. The WHO case definition guideline is used to categorize “alert,” “suspected,” “probable,” or “confirmed” cases. The typical clinical features consist of high fever of sudden onset in a contact. This is usually associated with cough, diarrhea, and bleeding manifestations and the patient quickly dies within days due to shock and multi organ failure. The challenge, however, is the presence of many tropical diseases that mimic this syndrome. Malaria for instance is endemic in Equatorial Africa, where most outbreaks occur. The sensitivity and specificity of the clinical

case definition as well as its positive predictive value is largely unknown from outbreak to the other. Confirmation based on laboratory ELISA and antigen tests equally has a very low positive predictive value of less than 50% [15]. This may be compounded further by a significant presence of Ebola and Marburg IgG antibodies among asymptomatic individuals in the rain forests of Central Africa. Sero-surveys in some countries in Equatorial Africa reveal that the Ebola virus IgG prevalence was 5.3% while for Marburg it was 2.4%. The pigmy population had a significantly higher IgG prevalence of 7.02% [32]. An even high ZEBOV specific seroprevalence of 19.4% was found near the rain forests in the Demographic Republic of the Congo [33]. Surveys in identified populations in Equatorial Africa have revealed significant prevalence of Ebola IgG antibodies among asymptomatic individuals [9, 33–35]. This suggests some cross-reactions or past mild infection with diverse filoviruses. The observation probably suggests frequent contact between human and less virulent strains. Thus, the management of outbreaks including the identification and isolation, discharge and care has real limitations. Therefore, it is desirable to concurrently determine the sensitivity and the specificity of these detection methods during ongoing outbreaks and refine the case definition. More sensitive noninventive methods of detection to support surveys in wildlife would support our understanding of the natural course of filovirus illness.

5. Challenges to food security

Food security is an issue to consider in view of the reported filovirus infection in pigs and bats. In some parts of Africa, bats are often eaten and fruits are a shared food source with wild animals. It has been reported that the Ebola virus has been found in frugivorous bats. These bats if they come into close contact with humans through the fruits such as coconuts, a shared food source, could pose a potential danger. Marburgvirus has also been isolated from orangutan primates in Indonesia [36]. Isolates of Ebola virus from wild apes also reveal genetic lineage and recombinants [37]. This interface makes it possible for the infection to be acquired from these suspected intermediate hosts or reservoirs. Infection to susceptible humans through the primary or intermediate reservoirs such as chimpanzees, pigs, and duikers or directly through the food source may contaminate the food chain and propagate the infection. The role of other suspected reservoirs including arthropod vectors, rodents, and plants [19, 38] while unlikely is unknown and should be studied.

6. Conclusion

Filoviruses are emerging infections that present considerable challenges in understanding their elusive ecology, transmission, and reservoirs particularly bats. Direct contact with infected blood and body fluids remains the major mode of transmission of both viruses. The discovery of new subtypes of Ebola and other viruses shows increasing diversity in the evolution of these viruses. The ecology and the evolving dynamics of these viruses need to be examined to identify those other related hosts and viruses. While it is generally accepted that the filoviruses are transmitted through direct contact, there is evidence that respiratory transmission through aerosols and droplets can be considered in massive outbreaks. While we also know that transmission does not place before symptoms emerge, additional data should refine the exact onset of infectiousness. The virus may be shed for some months post recovery through semen and breast milk among survivors.

The possible amplification of transmission by domestic or wild animals during the massive West African outbreak sheds some light on the role of such animal to human interface. The possibility of Ebola and Marburg entering the food chain and compromising safety should be assessed especially in pork and pork products. Case detection of index cases in emergencies presents a real challenge in low resource settings. The case definition of diagnosis and algorithms for management should be refined and validated regularly to improve on the positive predictive value of screening tests.

A global strategy for surveillance of filoviruses is required for a coordinated worldwide strategy and response that will mitigate the global impact of future outbreaks. Disease management needs evidence from ecological studies and prevention and control strategies should adopt One Health concept, which integrates animal and human health interventions to support early detection, surveillance, prevention, and control.

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