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Review Article

Marburg Virus Disease: An Emerging Public Health Challenge

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Abstract

Marburg Virus is a contagious virus belonging to the family Filoviridae, which is shared by Ebola Virus. It leads to a disease which is typically characterized by viral haemorrhagic fever (VHF). The infection can get systemic during the late organ phase, which eventually leads to multi-organ dysfunction, thereby making it a deadly disease. An important factor contributing to its tissue tropism is the Marburg Virus glycoprotein (MARV GP), while a host of nucleocapsid-associated as well as matrix-associated proteins contribute to its features of immune evasion and viral spread. Till now, all of the major outbreaks have been traced to African origins and efforts are being made to raise awareness regarding this emerging infectious disease. Prevention is dependent on early diagnosis or detection, which relies upon RT-PCR, Antigen ELISA, Antibody ELISA, etc., as well as protection against the natural reservoirs, the Egyptian fruit bat, and their droppings. Adequate protection and distancing from the infected vectors, the non-human primates (NHPs) is also crucial. This review discusses some key aspects of Marburg Virus and the disease that it causes, while also throwing light on prevention and control strategies, in the backdrop of the recent outbreak in Ghana. The review concludes by drawing a parallel between MARV and other bat-borne as well as RNA viruses, integrated with the selection pressure on this virus to delineate the potentiality of a future large-scale outbreak of MVD.

Keywords:- Egyptian fruit bat; Filoviridae; Immune evasion; MARV GP; NHP; Selection pressure; Tissue tropism; Vector; VHF

Introduction

Marburg Virus Disease (MVD) is caused by the pathogen Marburg Virus (MARV). It has been named after Marburg, a city in Germany wherein its first outbreak had occurred (alongside the Serbian city of Belgrade), and is a deadly virus that is one of the pathogens causing Viral Haemorrhagic Fever (VHF). The emerging and re-emerging infectious disease caused by this virus has led it to be categorized in the Category A Priority Pathogen list laid down by National Institute of Allergy and Infectious Diseases (NIAID) (Bente *et al.*, 2009). It belongs to the genus *Marburgvirus*, which in turn contains only one species, i.e. *Marburg marburgvirus*. The species majorly has two viruses- Marburg and Ravn, having a genetic divergence of 20% (ICTV. Genus Marburgvirus.). MARV shares the same family as Ebola Virus, i.e. Filoviridae, of the order Mononegavirales. Despite the observation that the Ebola virus has an R_0 value of 1.5-2.5 and the MARV has an R_0 value of 1.59, MVD is believed to be less contagious than Ebola (Ajelli and Merler 2012).

The genome of MARV consists of a negative-sense single stranded RNA, while the pathogen itself bears an envelope encapsidation. As indicated by the family name, it is a filamentous virus, having a genome that encodes for seven structural proteins, each playing distinctive role in MVD pathogenesis.

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The RNA genome of MARV is coupled with unique proteins, such as the nucleoprotein (NP), the L-polymerase or Large protein (L), viral protein 30 (VP30) and VP35- all together forming the nucleocapsid. This ribonucleoprotein complex is surrounded by a matrix (comprising of VP40 and VP24), followed by a lipid envelope bearing surface glycoprotein (GP) spikes (Olejnk *et al.*, 2019; Gordon *et al.*, 2019, ICTV. Genus Marburgvirus). The MARV GP is crucial in displaying cell and tissue tropism, as well as virus-host cell membrane fusion during pathogenesis. The GP is also believed to be responsible for immune evasion by neutralizing the anti-viral effect of tetherin, an interferon (IFN)-stimulated protein that prevents viral spread (Gordon *et al.*, 2019; Messaoudi *et al.*, 2015). VP40 is the vital virulence factor that can counteract the innate immune response of the host (Valmas *et al.*, 2010). It can also repress the host cell's response to IFN signalling during viral immuno-pathology (Valmas and Basler, 2011). VP35 is found to play multiple roles- it is a virulence factor that aids in immune evasion by impairing IFN response, and it is also important in the making of viral RNA (Messaoudi *et al.*, 2015). Simultaneously, VP24, the minor matrix protein, also contributes to repressing the IFN signalling-response of host cells (Messaoudi *et al.*, 2015). The L-protein or the polymerase is directly involved in the replication and transcription of the MARV genome (ICTV. Genus Marburgvirus).

Outbreaks and Epidemiology

The origin of major outbreaks of MARV across the globe has been traced to African countries. Some of the significant outbreaks are enlisted in Table 1.

Table 1: Major outbreaks of MARV in chronological order.

Month & Year	Location	Suspected Origin	Case-Fatality Rate	Strains	Epidemiology
August, 1967	Germany (Marburg) and Serbia/ Yugoslavia (Belgrade)	Uganda	23%	MARV Ci67, MARV Flak, MARV Hartz, MARV "L", MARV Porton, MARV Popp, MARV Rat, MARV Voe	Simultaneous outbreaks taking place in lab-workers handling African Green Monkeys imported from Uganda
February, 1975	South Africa (Johannes-burg)	Zimbabwe	33%	MARV Cru, MARV Hogan, MARV Ozo	A man with recent travel history to Zimbabwe (probably Chinhoyi caves), being admitted to a hospital in S. Africa. Transmission took place to his companion as well as a nurse
January, 1980 and August, 1987 respectively	Kenya	Nairobi, Kenya	50% and 100% respecti vely	MARV Mu and RAVV Ravn, RAVV R1	Recent travel history to Kitum Cave in Kenya's Mt Elgon National Park (apparently harbouring the bat reservoirs)
1990	Russia	Russia	100%	-	Laboratory contamination

1998-2000	Democratic Republic of Congo	Durba, DRC	83%	Many	Majority of the cases occurred in young male workers at a gold-mine in Durba, which was declared the epicentre of the outbreak
2004-2005	Angola	Angola	90%	MARV Angola	Suspected origin of the outbreak is Uige Province
2007, 2012, 2014 and 2017 respectively	Uganda	Kamwenge, Kabale, Kampala, Kween districts respectively in Uganda	25%, 27%, 100% and 75% respecti vely	MARV-01Uga 2007, RAVV-02Uga 2007,	Outbreak in gold and lead mines in Kamwenge district (Kitaka caves), and subsequent isolated cases in the respective districts
2021	Guinea	Gueckedou	100%	-	A single case was reported after death of the patient
2022	Ghana	Ashanti	Researc h On-going (suggest ed at 75%)	-	On July 7 2022, 2 fatal cases of MVD were confirmed by the Ghana Ministry of Health

Sources: Abir et al., 2022 and www.cdc.gov/vhf/marburg/index.html [accessed on 6th December 2022]

TRANSMISSION

Major outbreaks of the MVD have been reported in African countries, i.e. Democratic Republic of Congo, Gabon, Ghana, Kenya, Sierra Leone, South Africa, Uganda and Zambia (Abir *et al.*, 2022). Based on several epidemiological studies, it has been found that the transmission of MARV among humans is similar to that of Ebola virus, Bundibugyo virus and Sudan virus (Boadu *et al.* 2021; Amman *et al.*, 2015). Ongoing research, largely based on PCR-positive tests, has indicated that the major natural reservoir of MARV is the Egyptian fruit bat species *Rousettus aegyptiacus*, while *Hipposideros caffer* and few additional unclassified Chiropteran may also be considered as minor natural reservoirs (Abir *et al.*, 2022).

Various routes of bat-to-bat transmission have been indicated in scientific literature. The passage of MARV by the infected bats, in its urine as well as rectal and oral samples, is a prominent route. Other than this, reports of MARV being detected in blood samples of in-contact bats also exist. Together, these findings point towards 'horizontal transmission' of MARV from inoculum-harbouring bats to in-contact bats (Schuh *et al.*, 2017). A separate study has shown that MARV can also be transmitted 'vertically', alongside horizontal transmission, as indicated by the presence of virus in tissues such as salivary glands, lungs, intestines, kidneys, bladders, and female reproductive tract of inoculated bats (Paweska *et al.*, 2012). Few other hypothetical routes of bat-to-bat transmission have also been suggested-i.e. biting, sexual contact, hematophagous arthropods (Schuh *et al.*, 2017; Amman *et al.*, 2012; Amman *et al.*, 2021).

The reservoir-to-host transmission of MARV involves 'intermediate hosts', which are non-human primates (NHPs) and animals that are hunted for bush-meat. They are the main 'vectors' in MARV transmission. However, the exact route of reservoir to human host transmission of this virus is yet to be

elucidated (Kortepeter *et al.*, 2020; Jones *et al.*, 2015). Plausible routes of transmission from reservoirs to humans as well as NHPs suggested in various studies are- bat saliva, urine, faecal droppings, MARV-contaminated fruits, etc. (Schuh *et al.*, 2017; Amman *et al.*, 2021). Among human hosts, MARV may be transmitted through sexual intercourse, as substantiated by the presence of viral antigens in the semen of infected human males (Kortepeter *et al.*, 2020). Other than this, direct contact with body fluids (e.g. saliva, urine, faeces, teardrops, mucus, breast-milk) of infected individuals is also a concerning route. Transmission to foetus via placenta has also been pointed by case studies (Bebell and Riley 2015). Inadequate managing of MARV-infected corpses is also a threat area as it may lead to irresponsible transmission of MARV. Fomite- or aerosol- borne transmission of this virus is also indicated in certain studies (Johnston *et al.*, 2015; Piercy *et al.*, 2010).

Vaccination Strategies And Rapid-Response Control of MVD

The prevention and control of MARV is an on-going area of research and discussion, owing to the fact that the exact transmission route from reservoirs or NHPs to susceptible human hosts is yet to be elucidated. Several preventive strategies have been suggested: (i) avoiding fruit bats and infected NHPs; (ii) total quarantine of infected humans; (iii) care-givers should avoid direct physical contact with infected humans, by using gloves, masks, gowns etc.; (iv) proper disposal, and if necessary, sterilization of needles, other medical equipment/accessories and patient excretions; (v) spreading awareness among vulnerable communities as well as health-care providers for better preparedness and participation in rapid-response control; (vi) quick and easy access to rapid-testing tools for early diagnosis of MVD; (vii) Bio-safety Level 4 laboratories should be used while dealing with suspected MARV samples (cdc.gov/vhf/marburg).

Members of Filoviridae are able to survive in liquid or dry material for many days. However, they are easily inactivated by physical treatments such as gamma irradiation, heating at 60ºC for 60-75 minutes, boiling for 5 minutes, and chemical treatments such as lipid-based solvents, sodium hypochlorite and other disinfectants (Feldmann *et al.*, 2019; Piercy *et al.*, 2010; Kuhn, 2008).

Till date, no licensed vaccine for MVD exists, although some cases have been under development for quite some time now. The outbreaks reported till today were controlled when the chain of transmission terminated either naturally or through implementation of public health and infection control measures. However, it is still worthwhile to consider developing an effective vaccine against MARV, keeping in mind the Angola outbreak of 2004-2005 (with a fatality rate of about 90%). This has led to the proposal of few mathematical models for an efficient vaccination drive (Qian *et al.*, 2022).

Discussion

Marburg Virus Disease is a re-emerging infectious disease of African origins, which often proves to be fatal. The diverse and sometimes inconspicuous nature of its infection route in humans, as well as the RNA-genome of MARV makes it a difficult viral disease to track and treat. It is believed that for the past couple of centuries, the viruses harboured in bats are facing an increased selection pressure due to the survival challenges faced by their natural reservoir, the bats. These challenges in turn, arise from various anthropogenic-activities such as deforestation and urbanization which leads to habitat-destruction, climate change, consumption of bats for meat, and generally increasing proximity between bats and the human hosts among several others (Bhattacharya *et al.*, 2020). Due to this, more virulent viral strains, having the potential for crossing species barrier (and consequently positive selection) are evolving. It is important to understand that bat-borne viruses exist as a large, dynamic population comprising of different strains coexisting in their Chiropteran mammalian host. Genetic events such as spontaneous mutations and recombination play a key role in the evolution of these viruses. These factors, coupled with the survival challenge to their bat hosts, put the viruses under extreme selection pressure and as such, only the best ones are positively selected in the race for survival (Klempner *et al.*, 2004; Bhattacharya *et al.*, 2020).

Even though there are only a handful of reported strains of MARV so far, we cannot fully exclude the possibility of more pathogenic strains (with increased potential for epidemics or pandemics) evolving from the existing pool, keeping in mind the increased number of epidemics and pandemics caused by RNA-viruses in the past one century. For instance, the 1918 avian flu pandemic caused by influenza A H1N1 strain, the 1957 pandemic caused by influenza A H2N2 strain and the 1968 pandemic caused by influenza A H3N2 strain all have their origins in the avian-native influenza A parental strain H5N1. This parental strain, as indicated by phylogenetic studies, had evolved to display greater pathogenicity and broader host spectrum, eventually crossing the species barrier; however, it is not clear, in which host species exactly did the recombination event and subsequent evolution occur (Klempner *et al.,* 2004). Nonetheless, these strains are presently naturally residing in human populations, implying that the evolution is likely to continue even if there is no or limited contact between the avian reservoirs and human hosts anymore. Similar is the case of the SARS CoV outbreaks of 2002 and 2019- namely the SARS CoV 1 epidemic and SARS CoV 2 [the infamous Covid 19] pandemic respectively. Both originated in China, supposedly because of evolution of virulent strains from a common SARS CoV in bats. These zoonotic viral strains could not only cross species barrier to infect human hosts, but also infect macaques and camels, indicating the diverse capability of binding to host cell receptors (Fouchier *et al.,* 2003; Bhattacharya *et al*., 2020). The human CoV 2 strain display significant homology with a bat CoV strain, indicating that both the bat strain as well as the human strain have been positively selected (Bhattacharya *et al*., 2020). Moreover, as is evident from the human-to-human transmission cases, these SARS CoV strains have now become well settled in the human population as well. These points potentiate the probability of further evolution of the SARS CoV strains that may culminate into another pandemic(s). Thus, the facts that MARV has an RNA genome, and has already evolved to include NHPs as their vectors indicate that it is also possibly likely to evolve further into a more pathogenic strain with broader host range.

The variety of symptoms that MARV can cause are attributed to a repertoire of functional molecules such as nucleo-capsid proteins, glycoprotein etc. Just like several other zoonotic viruses originating from bats (i.e. Hendra, Nipah, SARS CoV, MERS CoV, Ebola), MARV is also an RNA virus, which further complicates the process of vaccine-development due to the rapid mutability of RNA genome and subsequent phenotypic variations. So far, the control of the MVD largely hinges upon early detection and prevention strategies, as no effective vaccine has been launched yet. However, general awareness among people, particularly those who travel to or from reported zones of outbreak and their vicinity can prove to be helpful. Until a suitable vaccine arrives, preventive measures such as keeping safe distance from primate-inhabited sites, bats or both, use of cleanliness practices in quarantine sites, and careful handling of corpses of infected beings will be vital. Additionally, periodic surveillance and monitoring of the viral load in susceptible human populations, bat reservoirs and probable NHP vectors would be a good idea, so as to clearly assess the viral reserves in the society and then enable better equipment for rapid-response in case of a sudden outbreak. Although the patients suffering from the Ebola Virus disease, which is also of African origins, have similar ordeals as the MVD-inflicted patients, it is important to take into consideration the fact that there already exist some efficacious antivral medicines for humans against the Ebola virus; however, no effective medicine against the Margurg virus is presently known (Mulangu *et al.,* 2019; www.cdc.gov/vhf/marburg/treatment/index.html). Therefore, awareness, monitoring and rapid-response are the only few actions that can be undertaken to limit the spread of this virus in human population and manage an MVD outbreak in case it happens. And last but not the least, respecting the boundaries laid by nature is something which we humans have to take care of as a society, otherwise the viral spill-over from the reservoirs to human beings will continue till the human population load is naturally balanced out- as rightly predicted by the 18th century economist Thomas Malthus.

Conclusion

Among all the viral diseases of man, about 60-80 % are zoonotic, meaning that the causative viral agents are of animal origin. Bats, the Chiropteran mammals, are the acme of animals with zoonotic disease potential, and have consequently resulted in several large scale disease outbreaks spread across history. It is therefore vital to keep human-animal conflict issues in check, if mankind is to protect itself from more dangerous viral outbreaks. This is especially true for viruses originating in bats, because of the rise in selection pressure on bat species. The loss of their natural habitat is one of the plausible causes behind viral spill-over from the primary reservoirs to the human and other animal populations. Not only this, the ability to co-exist and co-evolve with their natural reservoirs helps these zoonotic viruses to be positively selected, an event due to which they emerge into more virulent strains, from a previously non-virulent or less virulent strain.

MVD is an emerging infectious disease with the potential to threaten public health security because of the diverse as well as severe nature of its pathogenesis in humans. The fact that MARV is majorly a bat-borne virus, that uses NHPs as a vector-host is alarming, and as such raises the concern of taking appropriate control or preventive measures. Owing to its inconspicuous route of human infection, it may not be possible to predict, and thereby prepare for a likely outbreak. Moreover, the lack of an effective vaccine presently, also contributes to the lingering threat. In such a scenario it is necessitated to implement combinational method of disease management and control. Such steps as sustained viral surveillance in susceptible populations of primary and additional reservoirs, as well as sero-epidemiological survey of reservoir and host of MARV endemic regions and international travel and trade routes may prove to be valuable. It will help in formulating area-wise strategy to prevent and control MARV disease outbreak in future, if any.

Conflict of Interest

The author(s) declare that they have no competing interests**.**

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