



THE MARBURG VIRUS DISEASE: A PROSPECTIVE

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ABSTRACT

Marburg Virus Disease is included in the WHO list of diseases that could cause future outbreaks and Epidemics. It causes hemorrhagic fever and has shown high fatality rate. A number of outbreaks have happened since its emergence in 1967, including the recent one in Tanzania and around African subcontinent on February-May 2023. This article looks at the disease from its emergence, history of outbreaks, clinical features of the disease like mode of transmission, symptoms, diagnosis, and treatment options.

Key Words: Marburg Virus Disease, Clinical significance.

INTRODUCTION

MARBURG VIRUS DISEASE

Marburg virus disease (MVD) is a severe, acute, and rarely occurring human disease caused by the Marburg virus. It affects people and non-human primates. The virus, belongs to the same family as the Ebola virus can cause severe viral hemorrhagic fever in humans with an average case fatality rate of around 50%. ¹

The animal reservoir for Marburg viruses is Egyptian rousette bats that is prominently found across African subcontinent. ²

HISTORY OF MARBURG VIRUS DISEASE (MVD)

The first outbreak of MVD was reported in August 1967 in Marburg an der Lahn and Frankfurt am Main, West Germany among laboratory personnel's who were involved in the manufacture of polio myelitis vaccine. Thus, it was named after the city as Marburg virus disease. Simultaneously another outbreak of the same disease was observed in the Institute of Virology, Vaccines and Sera "Torlak", Belgrade, Serbia. Retrospective studies were conducted on the two outbreaks and conclusions were drawn. It was found out that the outbreaks were associated with procedures that were carried out for the establishment of primary grivet cell cultures using tissues from grivets (*Chlorocebus aethiops*) which were imported from Uganda. The virology institute in Belgrade received shipments from Uganda which were routed via London and Germany between 18 July to August 1967. Within these shipments, it was reported that 12 animals died during the shipment process. ^{2,3}

Subsequently, various cases of outbreaks were reported around the globe including in: Angola, the Democratic Republic of the Congo, Kenya, South Africa and Uganda. The various outbreaks that have occurred over the time are enlisted as below. ^{3,4}

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Table No 1: Reported outbreaks of Marburg virus disease (MVD)

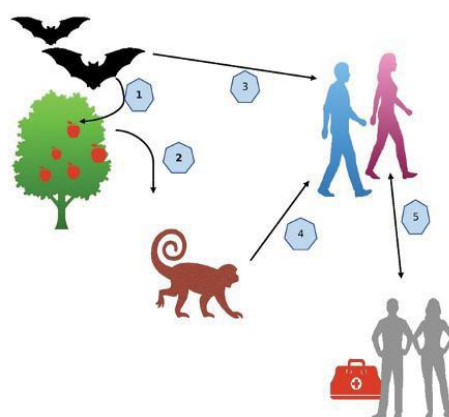
Year	Country	No. of cases	No. of deaths	Fatality rate (%)
1967	Germany	29	7	24
1967	Serbia	2	0	0
1975	South Africa	3	1	33
1980	Kenya	2	1	50
1987	Kenya	1	1	100
1998-2000	Democratic Republic of Congo	154	128	83
2005	Angola	374	329	88
2007	Uganda	4	2	50
2008	United States of America (ex-Uganda)	1	0	0
2008	Netherland (ex-Uganda)	1	1	100
2012	Uganda	15	4	27
2014	Uganda	1	1	100
2017	Uganda	3	3	100
2021	Guinea		1	100
2022	Ghana	3	2	66.7

Equatorial Guinea Outbreak Update

The Marburg viral illness (MVD) was first reported in Equatorial Guinea on February 13, 2023, by the government of that country (GREG). Numerous provinces, including Kie-Ntem, Littoral, and Centro Sur, reported cases. On May 15, the authorities said that the outbreak was over, noting 16 confirmed cases and 12 fatalities. On June 8, 2023, the World Health Organization proclaimed the outbreak to be finished, 42 days after the final patient was released from the hospital.⁴

TRANSMISSION

Marburg virus transmission illustrated in Figure 1.

**Fig No 1: Marburg Virus-Transmission.**

(1) & (2) Transmission of virus to Cercopithecoidea and Hominidae (monkeys) through the bite or partial chewing of fruits infected by bats' saliva; (3) direct human infection caused by the Marburg virus that bats shed after invading caves and other bat habitats; (4) Human-to-Monkey transfer via interactions; (5) Human-to-human transmission via physical touch.⁵

It was initially spread from the animal host to human beings. Retrospective studies and researches have shown that the virus is present in oral secretions, urine and feces of infected Egyptian rousette bats (*Rousettus aegyptiacus*, is a cave-dwelling bat found widely across Africa). The bats which were infected with the virus did not show any signs of the disease.^{3,5} By considering the cases of tourists visiting Uganda in 2008, it was detected that unprotected contact with infectious bat feces or urine droplets were the most likely routes of infection.⁶

Following the first transmission from animal to human beings, human-human transmission occurs through direct contact. The contact can happen through broken skin and mucous membranes in the eyes, nose, or mouth in many ways including:

- a) Spread through blood or bodily fluids, such as amniotic fluids, breast milk, urine, sweat, or stool.

- b) By having infected semen during oral, vaginal, or anal sex with a guy who has just recovered from a Marburg virus infection and is symptom-free.
- c) Transmission while handling objects like medical instruments, needles, syringes, and patient personal items that are soiled with bodily fluids from the infected patients or dead bodies before burial. ⁴

SIGNS AND SYMPTOMS

The virus takes two to twenty-one days to incubate. Suddenly after that symptoms appear which include: fever, chills, headache, and myalgia. It is observed that many patients develop hemorrhagic manifestations between 5-7 days. Almost around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the torso may occur. Other symptoms observed include nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea. ⁶ Symptoms become increasingly severe and can include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multi-organ dysfunction. ⁴ With the involvement of CNS in the infection cycle there can be occurrences of confusion, irritability and phases of aggression. It has also been reported that orchitis can occur occasionally during the late phases of infection. Death can occur between 8-9 days after onset of symptoms in fatal cases. It occurs generally after severe hemorrhage, blood loss and shock. ⁷

DIAGNOSIS

Diagnostic tests carried out for Marburg Virus Disease include:

- Antibody-capture enzyme-linked immunosorbent assay (ELISA).
- Antigen-capture detection tests.
- Serum neutralization test
- The RT-PCR assay, which uses reverse transcriptase polymerase chain reaction.
- Electron microscopy.
- Virus isolation by cell. ^{4,6}

MVD diagnostic techniques include isolation of the virus, reverse transcription-polymerase chain reaction (RT-PCR), antigen detection, serology, and immunohistochemistry. It has been demonstrated that NP, L, and GP gene-targeting molecular techniques (RT-PCR, nested RT-PCR, and real-time quantitative RT-PCR) are sensitive, specific, and useful for diagnosing MVD. ⁸

TREATMENT

Treatment possibilities for Marburg virus sickness have developed more slowly. ⁴ Currently no specific treatment options exist for MVD. Supportive care which include-rehydration with oral or iv fluids, maintaining oxygen level, replacement of blood, blood pressure monitoring and maintenance are utilized along with treatment for specific symptoms. ⁴ Prevention of MVD is based largely on avoidance of direct contact with infected people or contaminated materials. ⁶

No Marburg vaccines are approved worldwide. Phase I clinical trials are underway for three potential Marburg vaccines (cAd3, MVA-BN-Filo, and MARV DNA), while a Phase 2/3 clinical trial is planned for MVA-BN-Filo. Also, during clinical trial, it was observed that DNA vaccines against filoviruses showed limited immunogenicity. ⁹

Pharmaceuticals being developed to fight MARV include immunotherapeutic, phosphonodiamidite morpholino oligomers, lipid-encapsulated short interfering RNAs, small molecule inhibitors, interferons, and antiviral nucleoside analogues. There is no proof that favipiravir and remdesivir would be helpful in humans, although they do seem to be helpful in non-human primates. ¹⁰

PUBLIC HEALTH CONTROL MEASURES

Cutting off direct human-to-human transmission is the primary objective of managing an MVD outbreak. The outbreak control plan includes early discovery and systematic quick isolation of cases, contact tracing and close monitoring of people at risk, appropriate personal protection, safe burial practices, and increased community awareness of infection risk factors. In prior outbreaks, it has been demonstrated that the infected patients should be isolated along with suitable infection prevention and control measures effectively stops the spread of MARV and EBOV. ^{11,12}

Wearing personal protective equipment is required for everyone who works in the isolation area, launders possibly infected linens, disinfects objects or homes, transfers patients, or arranges safe burials. ¹² The greatest prevention and control methods for MARV are barrier nursing practices, which include the use of gowns, gloves, masks, face shields, or goggles to prevent contact with blood or bodily fluids.

Social mobilization and early, culturally appropriate community engagement are essential for bolstering outbreak response efforts and raising the awareness of MARV risk factors and personal protective measures among impacted populations, especially with regard to safe and respectable burial practices.

It is advised to stay away from any type of close contact with wild animals, including monkeys, forest antelopes, rodents, and bats, both dead and alive, as well as the manipulation or consumption of any kind of bushmeat. Other habitats that may be populated by bats include caves or mines in areas/countries where MVD has been reported. ^{13,10}

PREVENTION, PERSONAL SAFETY AND INFECTION CONTROL

Filovirus transmission should be reduced by coordinated, team-based interventions centered on case identification and surveillance, case treatment and isolation, social/community mobilization, and education. According to VHF protocol, patients should be segregated in a single room with a separate restroom as soon as the diagnosis of MVD is suspected, and the necessary actions should be taken. Because they are more likely to be exposed to infectious blood and bodily fluids, caregivers and healthcare workers (HCWs) who have intimate contact with patients are more at risk of developing motor vehicle disease (MVD). Workers in laboratories run additional risks. [4] It is necessary to use barrier nursing techniques to lower the risk of infection among healthcare workers. Procedures that produce aerosols ought to be avoided. It is best to steer clear of using needles and other sharp things. Any object in the isolation ward, including human excreta, needs to be cleaned with a bleach solution at a ratio of 1:10 before being disposed of. ¹²

The World Health Organization advises recovered male patients to engage in safe sexual behavior for at least a year following their clinical recovery, provided that MARV persistence in their semen has not been ruled out. [14] There is no set amount of time that separates the two tests.

It is important to avoid making any touch with the patient's body or fomites when the body is being buried. Conventional burial practices involve decontaminating the body with a 1:10 bleach solution and placing it in a body bag. After that, the body bag is sealed and the exterior of the bag is similarly cleaned. ¹²

As of yet, there is no authorized vaccine against MVD. Phase 1 clinical trials are underway for a number of potential MARV vaccines, including cAd3, MVA-BN-Filo, and MARV DNA. ^{14,15,16} There have been few trials for MARV, although various adenovirus-based vaccines have been investigated for EBOV. Serotype 5 (rAd5) recombinant adenovirus vaccines are most frequently delivered using this vector. Complex Adenovirus (CAVax) platform uses five filovirus antigens. These comprise two NPs, MARV-Musoke and EBOV, and three GPs, Sudan virus (SUDV), EBOV, and MARV (Ravn, Musoke, and Ci67 strains) ⁵⁶. A chimpanzee adenovirus serotype 3 vector vaccine (cAd3) MARV vaccine is presently being tested in a Phase 1a clinical trial. The modified vaccinia Ankara vector vaccine (MVA-BN-Filo), which is undergoing a Phase 2 clinical study, contains EBOV, SUDV, MARV, and Tai Forest NP. ¹⁶ After either primary or alternative boost, sustained EBOV GP immunity was seen; however, the response to MARV antigens has not yet been assessed. ¹⁷ DNA vaccinations have demonstrated minimal immunogenicity in clinical trials, despite the fact that they may induce humoral and cellular immunity in non-human primates. MARV-Musoke GP and MARV-Angola GP protected against homologous challenge and elicited an IgG response in cynomolgus macaques. ^{18,19} The MARV DNA plasmid vaccination (VRC-MARDNA025-00-VP) expressing MARV Angola DNA has finished phase 1b clinical investigations. ¹⁰ To far, no Phase 1 clinical studies have been undertaken on MARV, despite the fact that the recombinant vesicular stomatitis virus (rVSV) vaccine that incorporates MARV GP instead of its innate surface membrane GP appears promising. Vaccines against MARV VP40, GP, and NP have been produced using MARV virus-like particles (mVLP). A mVLP vaccination against the isolates of MARV-Musoke, Ravn, and Ci67 was evaluated in non-human primates, and antibody responses to all three strains were noted. ²⁰

2. CONCLUSION

Recent outbreaks of the Marburg virus around African subcontinent have increased the awareness of research community towards this deadly virus disease. But the research done worldwide is very less comparatively and even though there are drugs and vaccines under trial, currently no specific vaccine or treatment exists for the disease. Understanding the disease pathogenesis and underlying mechanisms behind the infection has been one of the major reasons for the slow pace in developing effective agents against this disease. Therefore, more research work and studies need to be carried out to completely understand the pathogenesis and pathogen features and to develop an effective and specific treatment against the disease as there exists possibilities of future outbreaks.

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