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A Review on Marburg Virus: Another Zoonotic Pathogen

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A B S T R A C T

Following an outbreak in 1976, virologists in Marburg discovered the Marburg virus. Since 1967, two significant outbreaks of the Marburg virus (MARV) have occurred. They occurred in 1998 and 2004. A MARV infection causes a fatal severe hemorrhagic fever that affects organs and may cause death. Human-to-human transmission and exposure to fruit bats in mines and caves both played a significant part in the expansion of MARV epidemics in African nations. WHO estimates that there is a high probability of national spread and a moderate risk of global dissemination for the epidemic in 2022. Due to the high fatality rate of up to 90%, thorough research into MARV diseases (MVD), which are linked to MARV infection, is essential. Large MARV outbreaks are uncommon, thus clinical examinations frequently fall short of supplying the essential data necessary to decide how to treat the condition. To better understand this harmful virus and the infection it causes, we reviewed and compiled important data on MARV disease outbreaks, pathophysiology, and mode of transmission, Lab diagnosis, symptoms and management strategies in this study.

Introduction

Marburg virus (MARV) epidemics are lethal and have a high mortality rate. Since its coincident identification and characterization in 1967 in Belgrade, Yugoslavia; Frankfurt, Germany; and Marburg, Germany. Africa was the location of the bulk of MARV outbreaks. The main cause of MARV disease (MVD) is MARV, which is included on the NIAID Category A Priority Pathogen list (Bente *et al.*, 2009). MVD is lethal and frequently remains untreated in both humans and non-human primates (NHPs), causing hemorrhagic fever, organ dysfunction, infection of the spleen, brain, and renal tissues, as well as problems with coagulation throughout the body (Mehedi *et al.*, 2011; van

Paassen *et al.,* 2012). The Filoviridae family of viruses includes this one. Only the Marburg virus, sometimes known as the Marburg virus, belongs to this genus (Kuhn *et al.,* 2012).

The properties of MARV's human-to-human transmission are comparable to those of the more thoroughly studied Ebolaviruses, such as Ebola virus (EBOV) (Boadu *et al.,* 2021), Sudan virus, and Bundibugyo virus (Brian *et al.,* 2015). It has been challenging to identify the MARV's natural reservoirs because of the virus' erratic nature. However, persistent investigation and arduous efforts have identified the virus's natural sources, defining the method by which it spreads.

Genome and structure of Marburg virus

Six distinct morphologies, including filamentous, circular, U-shaped, and rod-like, are observed in pleomorphic viruses like MARV (Bharat *et al.,* 2011). MARV virions typically have an average diameter of 80 nm and a length of 790 nm, while their length varies greatly (Welsch *et al.,* 2010). The virion's surface is protected by spikes that are spaced around 10 nm apart and have lengths between 5 and 10 nm (Bharat *et al.,* 2011; Feldmann *et al.,* 1991).

Its RNA genome contains seven genes in the order 3'-NP-VP35-VP40-GP-VP30-VP24-L-5', which are encoded by a 19.1 kb non-segmented negative-sense virus (Fig.1). These seven genes have highly conserved transcription start and stop signals as well as exceptionally long noncoding nucleotide sequences at their 3' and 5' terminals (Feldmann *et al.,* 1992).

Outbreaks and epidemiology

The first MARV outbreak was reported in 1967 at Marburg, Germany, where researchers and lab assistants were experimenting with tissue from African green monkeys (*Chlorocebus aethiops*) that had been imported from Uganda in an effort to create polio vaccines (Feldmann *et al.,* 1996; Ristanović *et al.,* 1967).

Three people contracted the following MARV epidemic, which occurred in South Africa in 1975. The first patient caught the infection while travelling to Zimbabwe, and his travelling companion as well as a nurse did the same (Feldmann and Klenk, 1996; Gear *et al.,* 1975). In Kenya, a third MARV outbreak was detected in 1980. This outbreak involved a patient who contracted the virus after visiting the Kitum cave and a healthcare worker who contracted it while treating the patient (Smith *et al.,* 1982). A second MARV strain was discovered in Kenya in 1987 as a result of another minor epidemic (Johnson *et al.,* 1996). The following MARV outbreak, which was connected to 154 total infections, occurred in the DRC (Democratic Republic of the Congo) between 1998 and 2000 (Towner *et al.,* 2009; Colebunders *et al.,* 2007). The Uige region of Angola experienced a second, extremely serious MARV outbreak that started in October 2004 and continued until July 2005 (Nyakarahuka *et al.,* 2019).

The risk of 2022 outbreak

In 2022, the WHO predicts that there is a high likelihood of national spread and a low risk of global dispersion (WHO, 2022). Since the first Marburg virus patient had recently travelled from Ghana's Western area, which borders Côte d'Ivoire, to the Ashanti region, there is a chance that this outbreak would spread to neighboring countries. Like the Ebola virus, the Marburg virus travels from person to person by bodily fluids (Joi, 2022).

The Marburg virus is the main cause of the Marburg virus disease, which has a high fatality rate of up to 88%. The Marburg virus was the first filovirus to be identified eventually ongoing outbreaks in numerous European laboratories (Marburg virus disease, 2023).

In addition to Angola, MARV has been contracted in the DRC, Uganda, Zimbabwe, and Kanye's forests. The African green monkey that was the cause of the European outbreak in 1967 could have been obtained from a source in Uganda. This

particular case of the sickness spreading to 31 persons was brought through contact with the infected African green monkey (Marburg virus disease, 2023).

The biggest outbreak ever recorded till date occurred in Angola in 2005, with a total of 374 cases, 329 of which resulted in fatalities. In 2008, two isolated cases involving travellers from the Maragambo bush occurred in Uganda (Abir *et al.,* 2022). Three fatal Marburg virus infections were reported in October 2017 in eastern Uganda, close to the Kenyan border.

Some recent outbreaks include those in Ghana in 2022 after it reported its first confirmed cases, Guinea in 2021 when it reported its first confirmed cases, and Tanzania in February and March of 2023 when it reported its first confirmed cases (Malherbe and Strickland-Cholmley, 1971).

Reservoir

The Marburg virus (MARV) natural reservoir has been identified as Egyptian rousette bats (ERBs, *Rousettus aegyptiacus*), cave-dwelling fruit bats that are widespread in sub-Saharan Africa and portions of the Middle East. Marburg virus-ridden bats (Fig.2). When the Marburg virus becomes inflamed in primates, they may get seriously ill.

Mode of transmission

Direct touch with contaminated people, bats, fruit, and bodily fluids. Food that has been tainted by salvia or contaminated bat urine. Serious hemorrhagic signs affect a lot of patients (within 7 days). Using infected patient bodily fluids or by direct contact, an infection can spread from person to person (Fig.3).

Incubation period

The incubation period of MARV can be up to 3 weeks from the infection. The virus infection can show symptoms after 3 weeks of infection without showing any symptoms up to 3 weeks.

Sign and Symptoms

The signs and symptoms which arises following MARV infections are:-

Fever

Chills, Discomfort, severe head ache.

Severe haemorrhagic fever.

Symptoms also include inflammation of the pancreas, jaundice, weight loss, shock, liver failure and other severe infections.

Host cell pathology and pathophysiology

Rousettus aegyptiacus, also known as the Egyptian fruit bat, was found to be the animal reservoir for the virus, in which the virus replicates and sheds from bats (Malherbe and Strickland-Cholmley, 1971).

Marburg hemorrhagic fever (MHF) is caused by the MARV, which enters the body through damaged skin. MHF's most severe clinical symptoms include incorrect flu distribution, coagulation issues, shock, and numerous organ failures. Mononuclear phagocytic cells are the primary target of the Marburg virus, which causes cellular activity and allows damage to secondary targets such as endothelium cells (Abir *et al.,* 2022).

At the organ level, it appears that Marburg virus primarily targets the adrenal glands, the liver, and lymphoid tissues for replication in patients with the infection (Malherbe and Strickland-Cholmley, 1971; Guito *et al.,* 2021). The main targets for MARV entry at the cellular level are macrophages and dendritic cells. During the 1987 Kenyan outbreak, virions and antigens associated with the virus were identified using immunohistochemical and electron microscopy experiments (Guito *et al.,* 2021). Tissue damage and viral antigen presence are shown by light and electron microscopy, immune-histochemistry, and insitu-hybridization studies.

The Marburg glycoprotein (GP), which mediates and binds to entering host cells, is the most important adherence factor on the viral surface. Neutrophil inactivation and immunological suppression and evasion are also GP-related processes (Abir *et al.,* 2022).

Persistence

Marburg virus circulating in the blood of survivors is found in declining rate as the patient recovers. Sertolicells are the maincellular reservoir of persistent MARV intestes. In women who have been infected while they were pregnant virus persist in the placenta, amnioticandfetus. And women who are breastfeeding the virus persists in breastmilk (Guito *et al.*, 2021).

Mortality rate is high in case of Marburg virus but few of the patient's ion causes focal orchitis, germ cellloss, and abundant IgG antibody accumulation. Abundant IgG antibody accumulation infection. Marburg virus persist in the testicles of macaque survivors after treatment by disrupting tissue barrier integrity. Histological analysis of the testicles infected with Marburg virus revealed disruption of these miniferoustubules with presence of necroticdebris and inflammatory cells (Coffin *et al.,* 2018).

Pathogenesis

Although the data are limited, frequently fragmented, and occasionally perplexing, clinical examinations from episodes and outbreaks of human EBOV and MARV infections have offered crucial descriptive information on the pathophysiology and pathogenesis of these organisms.

In lab animals, extensive investigation has been done to a significantly greater extent. Researchers have used rodents, such as mice, guinea pigs, and hamsters, to research viral hemorrhagic fever (VHF), which is brought on by filoviruses (Barrientos *et al.,* 2007; Bary *et al.,* 1998; Warfield *et al.,* 2009). This section largely focuses on data gained from human clinical trials and experimental infections of nonhuman primates because data derived from studies utilizing rodants may not correlate with human disease or may be insufficient in identifying specific processes.

Marburg hemorrhagic fever pathogenesis

Dendritic cells and macrophages are the main targets of Marburg virus infection. Infection causes 'paralysis' of the innate response and dysregulation of lymphocyte costimulation in dendritic cells. Proinflammatory mediators like TNF-a are produced as a result of macrophage infection, and they could trigger bystander apoptosis in lymphocyte populations, leading to lymphopenia and immunosuppression. TNF-derived from macrophages also causes modifications in vascular permeability in addition to IL-6.

Additionally, the generation of TF by infected macrophages causes coagulation dysregulation (such as DIC), which is further exacerbated by hepatocyte infection and results in a reduction in the synthesis of clotting factors from the liver. Hypotension and metabolic issues are brought on by infection of the adrenal cortical cells, and these issues, together with immunosuppression and coagulopathy, play a part in multiorgan failure and shock.

Laboratory Diagnosis

Since the outbreak of MARV there are only few diagnostic techniques available for the detection of virus. Antibody detection IgG and IgM through ELISA can be carried out to rule out the infection following the development of symptoms. Real time PCR assays are also used for the early detection of virus using gene specific for MARV. However Cell culture is also employed for the identification of virus but this techniques is not so fast to detect early infection. Cell culture takes weeks to detect the growth of the virus. So we can focused on the development of techniques which are cost friendly and fast enough for the detection of virus as early as possible to rule out the infection.

Table.1 Filoviruses genes and the functions and molecular weight of gene products

Gene Order	Gene	Protein function	MW (kd)α
1	Nucleoprotein (NP)	Major nucleoprotein; RNA encapsidation	90-104
2	Virion protein (VP) 35	Polymerase complex cofactor; interferon antagonist	35
3	VP40	Matrix protein; virion assembly and budding; interferon antagonist	35-40
4	Glycoprotein (GP) Soluble glycoprotein (sGP) Small soluble glycoprotein (ssGP)	Virus entery (surface peplomer); receptor binding and membrane fusion Unknown Unknown	150-170[b] 50-55c 50-55c
5	VP30	Minor nucleoprotein; RNA encapsidation and transcription activation	27-30
6	VP24	Minor matrix protein; virion assembly; interferon antagonist [d]	24-25
7	Polymerase (L)	RNA-dependent RNA Polymerase; enzymatic component of Polymerase complex	~270

Fig.1 Genome structure of marburg virus

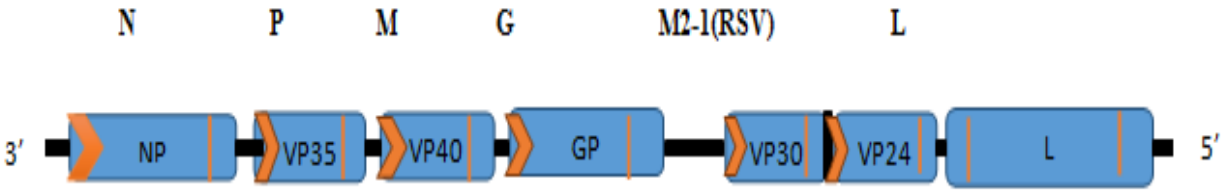


Fig.2 Egyptian rousette bats infected with Marburg virus

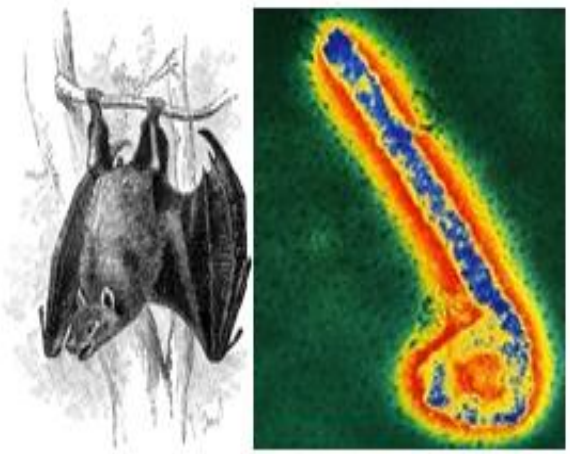
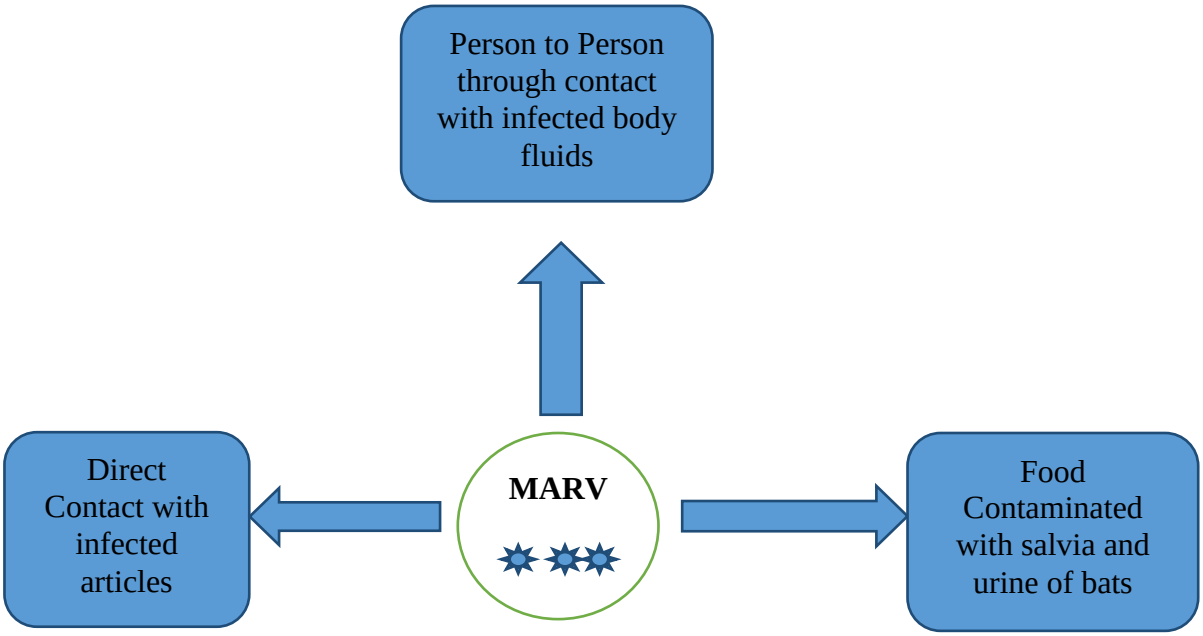


Fig.3 Transmission of marburg virus



Treatment

There are no antiviral medications or vaccines available. It is best to use supportive hospital care, which regulates blood pressure, monitors and balances oxygen levels in the blood, and balances bodily fluids and electrolytes.

Prevention and Control

The primary prevention strategies mostly focus on avoiding intimate contact with potential vectors—alive or dead—that may be able to transmit the virus, such as individuals who having contact with urine, vomit, saliva, blood, or other bodily fluids from people who have the Marburg virus. In order to reduce the appearance and formation of competent hemorrhagic fever epidemics, it is important that the natural reservoir of this virus must be identified. This will help advance public health initiatives and preventative measures. On the other hand rapid and reliable diagnostic technique can be developed for the early detection of the infections so as to isolate the infected person. However we can also focus onto the development of medication to treat the patients following infection.

New antiviral treatment based on the MARV can identified through proper research so as to treat the infected patients. We can also focused on the development of vaccine by identifying the consensus region in the genome of MARV so as it can be helpful in development of vaccine which can be effective even if slight mutation may happen during the virus transfer. Establish the vaccination and find-out the technique for the easily identification of the infection caused by the Marburg virus.

Clinicians should follow the protocol for diagnosis, reporting, and isolation of cases, maintain a high index of suspicion for this illness, as well as dispel public fears and misconceptions. Even though the disease in non-endemic nations has received attention globally, effort should be paid to controlling the disease in Africa, where the majority of deaths still occur. Future generations should remember to pay attention to neglected tropical illnesses.

Future perspective

Although research has made substantial advances in recent years, particularly in the development of improving our understanding of MARV ecology and the development of medical treatments and immunisation alternatives, much work remains to be done. Particularly, there are remarkable few data on the pathogenesis of MARV in either humans or animal models, and the few research that have been done have shown variations in the biology and pathogenesis of MARV and EBOV. Additionally, the increasing incidence of larger outbreaks shows that MARV could create a significantly greater threat to public health in the future than it currently (Feldmann, 2006).

The requirement for more clinical investigations during future MHF outbreaks to better understand pathogenesis in humans, faster and more precise diagnostic methods that can be used in both laboratory and field settings, increased efforts to develop new treatments and vaccines, as well as pushing currently promising products through the regulatory licencing process, are all emphasised by this.

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