Marburg Virus: A Potential Zoonotic Pathogen

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Lubabah Numan[1], Aziz Ul-Rahman[1*], Armain Syed[1], Mehwish Hussain[1*], Fakhar ul Din[1], Rida Ismail[1], Aroob Akram[1], Saleha Javed[1], Nusrat Shafi[2], Hafeez ur Rehman Ali Khera[3], Muhammad Asif Raza[1] and Junaid Ali Khan[4]

ABSTRACT

Marburg virus disease (MVD), a zoonotic illness transmitted chiefly through contact with the Egyptian fruit bat, has been a concern since 1967, notably with outbreaks in 1998 and 2004. Exposure to fruit bats in caves, alongside person-to-person transmission, fueled these outbreaks. MVD unfolds in three phases, marked by fever, muscle pain, aggression, and loss of appetite. MARV infection causes severe hemorrhagic fever, often leading to organ failure and a fatality rate of up to 90%. Due to rare outbreaks, comprehensive research for effective treatments is challenging. Significant outbreaks hit Marburg, Frankfurt, and Belgrade in 1967, with subsequent cases in Angola, DRC, Kenya, South Africa, Uganda, Guinea, Tanzania, and recently Ghana. WHO advocates bat avoidance, hygiene, PPE use, safe handling, screening, and awareness as preventive measures. Global collaboration among diverse experts is pivotal to prepare against MVD and mitigate potential global health threats.

Key words: Marburg virus, Egyptian fruit bat, zoonotic disease, transmission dynamics, global health initiatives, human primates.

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[1]Department of Pathobiology, Faculty of Veterinary and Animal Sciences, MNS University of Agriculture, Multan 66000, Pakistan
[2]Chaudhary Pervaiz Elahi Institute of Cardiology, Government of Punjab, Multan 66000, Pakistan
[3]Department of Clinical Sciences, Faculty of Veterinary and Animal Sciences, MNS University of Agriculture, Multan 66000, Pakistan
[4]Department of Pharmacology, Faculty of Veterinary and Animal Sciences, MNS University of Agriculture, Multan 66000, Pakistan
***Corresponding author:**mehwishhussain505@gmail.com, drazizangel@gamil.com

1. INTRODUCTION

Marburg virus (MARV) belongs to genus *Marburgvirus* under *Filoviridae* family and has potential to cause severe and deadly Marburg disease (MARD) (Bukreyev et al. 2014). MARV has been categorized as pathogen of category A by Centers for Disease Control and Prevention (CDC) and assigned as a Risk Group 4 Pathogen classification via World Health Organization (WHO) (Zhao et al. 2022). MARV is categorized as a zoonotic virus, indicating its ability to be transmitted from animals to humans. Reservoir host for MARV is Egyptian fruit bat (*Rousettus aegyptiacus*), which means that this particular bat species harbors virus without experiencing significant illness (Towner et al. 2009). Following initial zoonotic transmission from an infected animal to a human, subsequent transmission of virus is amplified through close human-to-human interaction. This transmission can take place through direct contact with bodily fluids or through contact with contaminated fomites, which refer to objects or materials that are likely to harbor infection (Dhama et al. 2022). Illness gives rise to hemorrhagic fever and disruptions in organ functionality, namely hepatic failure, brain infection, involvement of spleen, and issues affecting renal system. Additionally, complications related to coagulation are observed (Mehedi et al. 2011). Up until March 2018, a total of thirteen outbreaks of MARV disease had been documented, with the majority being taking place in sub-Saharan Africa. Among these outbreaks, the most substantial one occurred in Angola between 2004 and 2005, boasting a case-fatality rate of 90% (Amman et al. 2017). Given potential and significant threat MARV poses to public health and safety, it is crucial to implement systematic surveillance measures to effectively address its reoccurrence and increasing mortality rates associated with disease (Towner et al. 2006).

2. VIRAL GENOME AND STRUCTURE

The genome of MARV is approximately 19,000 nucleotides in length and undergoes transcription to produce eight significant sub-genomic messenger RNAs (mRNAs). These mRNAs are responsible for encoding seven structural proteins (Rougeron et al. 2015). Genomes of MARV consist of non-segmented negative-sense (NNS) RNA and exhibit a size range of 19,111 to 19,114 nucleotides (nts). These genomes are comprised of seven monocistronic genes arranged linearly. Each gene contains a highly conserved transcription start and stop signal, an unusually long 3' and 5' untranslated region, and an open reading frame (ORF). Genes are separated by short intergenic regions, which can vary in length from 4 to 97 nts. Core of Marburg virus particles is ribonucleoprotein complex (known as nucleocapsid) and consists of RNA genome, which is tightly associated with nucleocapsid protein sand tubular structures formed by this nucleocapsid within virus. Outer diameter of these structures is 45-50 nm, with an electron-dense central axis measuring 19-25 nm (Fig. 1) (Tiwari et al. 2018).

This genomic organization is a characteristic feature of MARV and is important for expression of individual viral genes. The 3' and 5' ends of viral genome contain extracistronic regulatory regions that play crucial roles in transcription and replication. These regions contain cis-acting signals, including transcription and replication promoters, which are essential for viral gene expression and genome replication. Non-segmented negative strand (NNS) RNA viruses generally have two types of genomic replication promoters including a bipartite promoter found in paramyxoviruses of *Paramyxovirinae* subfamily, and a more compact and continuous replication promoter observed in rhabdo- and pseudo viruses (Morrison et al. 2003; Easton et al. 2004).The bipartite promoter configuration found in *Paramyxovirinae* subfamily is connected to the "rule of six," i.e., the entire genome length must be a multiple of six. The identification of a bipartite structure in the mapping of the MARV genomic replication promoter was unexpected, considering the non-compliance of filoviruses with the rule of six. Genomic replication promoter of MARV consists of two elements. First element is located at the 3' end of the genome, known as leader, and contains initial promoter region. MARV's glycoprotein, GP,

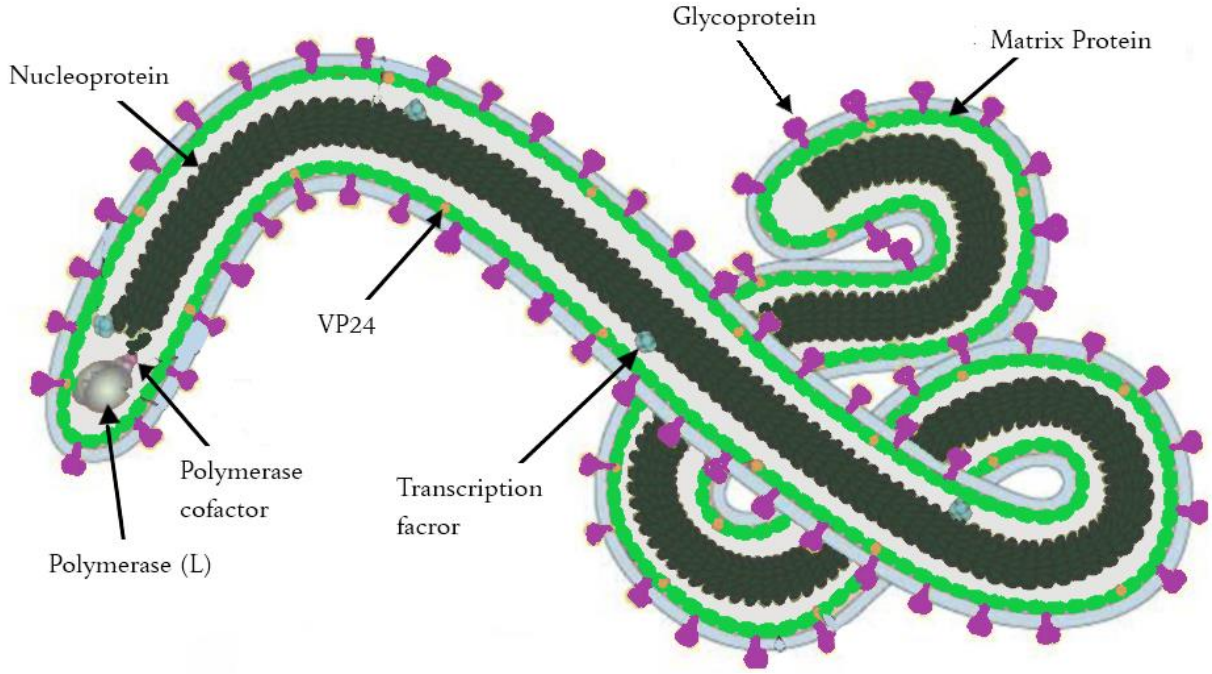

Fig. 1: Structure of Viral genome: The nucleoprotein enwraps genomic and antigenomic RNAs. VP24 is commonly referred as second, minor matrix protein. In event of an infection, VP24 plays a significant role in release of viral particles. It is encoded by fourth gene, glycoprotein is a single surface protein that facilitates attachment to target cells and aids in virus entry in form of homotrimeric spikes. Encoded by third MARV gene, matrix protein serves as counterpart of M proteins found in other NNS RNA viruses. Transcription factor proteins form a tight association within nucleocapsid by binding to NP. Polymerase cofactor protein functions as polymerase cofactor and is vital for both transcription and replication processes. Primary constituent of MARV polymerase complex L is estimated to have a molecular weight of 267 kD.

is encoded by fourth gene and plays a crucial role in attaching to target cells and facilitating virus entry. GP is a type I transmembrane protein that is incorporated into viral envelope as trimeric spikes (Raoul et al. 2019).

Precursor GP of MARV divides into two disulfide-linked subunits: GP1 (160 kD) and GP2 (38 kD). GP1, which forms ectodomain, is responsible for binding to entry factors and receptors, while GP2, which contains fusion peptide, mediates fusion of the viral and cellular membranes (Pigott et al. 2015). Domain of GP2 contains 30 amino acids, which are necessary for incorporation of GP. Cytoplasmic tail of GP2 enhances viral entry efficiency by maintaining structure of the ectodomain. The region responsible for receptor binding in MARV GP was identified within the amino-terminal portion of GP1, covering amino acids 38 to 188 residues (Kudo et al. 2020). On other side, highly glycosylated mucin-like domain is not essential for virus entry.A significant stage in the entry process of MARV involves the proteolytic activation of GP1 through endosomal proteases. This activation, in turn, enables the binding of the receptor binding region to the endosomal entry factor known as the Niemann-Pick C1 protein (Brauburger et al. 2012).

3. HISTORY AND GEOGRAPHICAL DISTRIBUTION

MARV has fatality rate of 24 to 88 % (Abir et al. 2022). During initial outbreak of Marburg hemorrhagic fever (MHF) in 1976, the first six patients were found to have been working in a plant that was believed

to be infested by insectivorous bats. This provided evidence that bats could be a source of human infection in MHF outbreaks (Languon and Quaye2019). In Durba outbreak, it was further confirmed that bats served as a source of human infection. During previous outbreak, at least nine different genetic variations of MARV were identified among affected individuals, indicating genetic diversity within virus population (Swanepoel et al.2007).Recently, evidence has emerged of six additional mutations in bats, providing support for theory that there may be additional variants of virus that have gone unreported. This is likely due to limitations of laboratory testing, which has typically focused on a small number of individuals. To sustain multiple genetic virus variants, there needs to be a substantial host population with ongoing accomplishment by migration or reproduction of sensitive individuals (Amman et al. 2020).
After initial identification in 1967, there was an eight-year period in which MARV remained dormant. However, in 1975, an Australian teenager who had moved to Zimbabwe was divulged to a sanatorium in South Africa, exhibiting indications evocative of those examined in 1967 epidemic in Europe. This case brought attention back to MARV (Slenczka and Klenk2007). From 1975 to 1985, there were sporadic outbreaks of the MARV on African continent, affecting only a small number of individuals. Mortality rates associated with MARV disease were low. Consequently, MARV was initially considered to be less threatening. However, in 1987, an outbreak occurred in Nairobi, Kenya, with the mode of origin traced back to Mount Elgon National Park (Petersonet al. 2006). In 1988 and 1990, there were outbreaks of MARV in Koltsovo, Soviet Union (now Russia), with suspected origin being laboratory infections resulting from unspecified breaches in safety requirements (Roffeyet al. 2002).
MARV re-emerged in two significant waves: from 1998 to 2000 in Democratic Republic of the Congo (DRC) (Bausch et al. 2006), and then again from 2004 to 2005 in Angola, Western Africa (Towner et al. 2006). These outbreaks highlighted the MARV as a significant threat to public health (Feldmann 2006). During MARV outbreaks from 1998 to 2000 in the DRC, it was discovered that 9 distinct virus modifications were moving among affected sufferers, indicating multiple independent introductions from the natural reservoir into human population (Languon and Quaye 2021). Table 1 highlighted the various outbreaks of Marburg virus from 1967-2023 in different regions of the world.

4. TRANSMISSION ROUTES

Previous investigations have highlighted several pathways for bat-to-bat transmission. Notably, excretion of MARV through urological, anal, and spit samples by infected bats represents a significant route of transmission (Abir et al. 2022). Additionally, there have been reports of MARV detection in blood samples from bats that had close contact with infected individuals. Collectively, these findings suggest a form of "horizontal transmission", where MARV is transmitted from bats carrying the pathogen to other bats nearby (Schuh et al. 2017). A distinct investigation has revealed that in addition to horizontal transmission, MARV can also be passed "maternally," as evidenced by inclusion of the virion in multiple tissues such as parotid glands, thoracic organs, bowels, nephritic organs, and female reproductive tract of bats that were deliberately inoculated with MARV (Pawęska et al. 2012). A few other theoretical pathways have been proposed, including biting, sexual contact, and transmission through hematophagous arthropods (Dhama et al. 2022).
Transmission of MARV from reservoir to host entails utilization of "intermediate hosts," which primarily consist of non-human primates and animals hunted for exotic meat. These intermediate hosts play a pivotal role as primary "vectors", facilitating transmission of MARV (Chakraborty et al. 2022). Nevertheless, the precise mechanism of transmission from reservoir to human hosts in the case of this virus remains to be fully understood. Potential pathways of transmission from reservoirs to both humans and non-human primates, as indicated by diverse studies, encompass contact with bat saliva, urine, fecal droppings, and consumption of fruits contaminated with MARV (Fichet-Calvet et al. 2014).

Table 1: Outbreaks of Marburg virus from 1967-2023 in different countries

Country	Number of cases	Year(s)	Reference
Germany	30	1967	Martini et al. 1971
Yugoslavia (now Serbia)	2	1967	Martini et al. 1971
South Africa	3	1975	Conrad et al. 1978
Kenya	2	1980	Smith et al. 1982
Kenya	1	1987	Johnson et al. 1996
Soviet Union (now Russia)	1	1988	Kuhn 2008
Soviet Union (now Russia)	1	1990	Nikiforov et al. 1994
Democratic Republic of the Congo	154	1998-2000	Bausch et al. 2006
Angola	252	2004-2005	Ligon 2005
Uganda	4	2007	Adjemian et al. 2011
USA	1	2008	Sah et al. 2022
Netherlands	1	2008	Timen et al. 2009
Uganda	1	2014	Luke et al. 2014
Zimbabwe	3	1975	Paassen et al. 2012
Uganda	1	2008	Stroher et al. 2001
Colorado	1	2008	Fujita et al. 2008
Ghana	2	2022	Jack et al. 2022
Russia	1	1991	Kimman et al. 2008
Russia	1	1995	Ignatye et al. 1996
Uganda	15	2012	Gear et al. 1975
Uganda	4	2017	Nyakarahuka et al. 2019
Guinea	1	2021	Aborode et al. 2021
Tanzania	8	2023	Larik et al. 2023
Equatorial Guinea	9	2023	Sohan et al. 2022
USSR	1	1990	Nikiforov et al. 1994
USSR	1	1988	Deb et al. 2023

Within human hosts, MARV can be transmitted through sexual intercourse, as evidenced by identification of viral antigens in the ejaculate of ailing males (Coffin et al. 2018). Additionally, direct contact with body fluids such as teardrops, mucus, and breast milk of infected individuals is also considered asa significant route of transmission (Shifflett and Marzi 2019). Case studies have also indicated the possibility of transmission to the fetus through placenta (Bebell and Riley 2015; Schwartz et al. 2019; Coler et al. 2022). Improper handling of MARV-infected corpses poses a significant risk as it may result in irresponsible transmission of virus. Furthermore, certain studies have suggested the potential for fomites or aerosol-borne transmission of virus (Leffel and Reed 2004; Dobler et al. 2012; Al-Moraissi et al. 2022).

5. SUSCEPTIBLE TARGET HOSTS

MARV has been found to have bats as central reservoirs and natural hosts. Specifically, Egyptian fruit bat (*Rousettus aegyptiacus*), belonging to *Pteropodidae* family of fruit bats, is considered as a primary reservoir for the MARV. Bats can carry the virus without showing symptoms of illness and may transmit it to other species, including humans. Close association between bats and MARV highlights importance of understanding the role of these natural hosts in transmission and spread of virus (Towner et al. 2009; Sah et al. 2022). Correct MARV varies in type and is inaccessible to various bat species in different African countries. In Kenya, Sierra Leone, Zambia, Uganda, Gabon, South Africa, and Leone, RNA of MARV is distinguished within bats (Pawęska et al. 2020). In 1999 in DRC, 12 MARV strains were obtained

from bats belonging to Chiroptera order, although specific species were unidentified. In 2007 in Uganda, one strain was acquired from *Hipposidero scaffer*, a bat species. These findings highlight the role of bats as reservoirs for MARV (Guito et al. 2021) and geographic diversity of virus strains circulating among bat populations. Indeed, MARV has been detected in blood and oral samples of bats that have come into contact with infected MARV positive bats. Virus has been found in various tissues of infected *Egyptian Rousettus* bats, including the rectum, salivary glands, urine, intestines, lungs, bladder, kidneys, and female reproductive tract (Schuh et al. 2017).

Consumption of bush meat from infected animals and handling of contaminated fruits that carry MARV are considered primary sources of transmission to non-human primates and humans, who are accidental hosts of virus (Amman et al. 2015). In the northeastern region of DRC, investigations have been conducted to identify reservoir hosts for MARV, focusing on local wildlife, including bats. From 1998 to 2000, there were outbreaks of Marburg hemorrhagic fever (MHF), and during this time, investigations were undertaken to study the presence of MARV in bats. Antibodies towards disease were noticed in serum in 20.5 %of fruit bat species and 9.7 %of one insectivorous species (Abir et al. 2022). Additionally, nucleic acid of MARV originated in twelve bats; encompassing 3.0 to 3.6 %of two insectivorous bat species and one species of fruit bat. However, efforts to segregate virus from these bats were not productive (Swanepoelet al. 2007). These findings suggest potential involvement of bats as reservoir hosts for the MARV, although supplementary learning is required to comprehend exact responsibility, they play in transmission dynamics of virus.

6. CLINICAL SIGNS AND SYMPTOMS

MVD symptoms have been mainly documented in three major reported outbreaks (Slenczkaand Klenk 2007). Incubation period for MVD, based on most reported cases of exposure and disease, ranges from 3 to 21 days. However, actual duration of incubation period can be modified by route of infection. MVD follows a three-phase progression. First phase is known as Phase of Generalization (Days 1-4), and symptoms include high fever (39-40°C), chills, muscle pain, and extreme fatigue. Gastrointestinal symptoms such as anorexia, abdominal discomfort, nausea, vomiting, and watery diarrhea may also occur during this phase (Asad et al. 2020). These gastrointestinal symptoms can be managed with various treatment options to provide relief to patients. Within first 4-5 days after surgery, patient developed symptoms of enanthem (a rash inside the mouth), dysphasia (difficulty swallowing), and pharyngitis (a sore throat) (Elsheikh et al. 2023).

Second phase is known as early organ phase (Day 5-13), during which patients may experience a range of symptoms. These include high fever, aggression, delirium, confusion, and irritability, which are neurological symptoms commonly observed during this phase. In addition, abnormal vascular permeability can occur, leading to symptoms such as conjunctival injection (redness of the eyes) and edema (swelling). Patients may also present with bleeding manifestations as ecchymoses (bruises), hematomas (collections of blood), bloody diarrhea, melena (black, tarry stools), and mucosal bleeding (Paassen et al. 2012).These symptoms are indicative of severe systemic effects of disease, including vascular dysfunction and coagulation abnormalities. Prompt medical attention and supportive care are crucial to manage these complications and improve patient outcomes. Third and last phase known as Late Organ or Convalescence Phase (Day 13+), in which organs such as liver, pancreas, and kidneys can be significantly impacted. Virus can cause damage to these organs, resulting in their dysfunction and contributing to overall severity of condition (Bente et al. 2009).

MARV predominantly induces a highly severe form of hemorrhagic fever, characterized by exceptionally high case fatality rates that often surpass 80 % (Hensley et al. 2005). In 1987, an investigation conducted in Kenya employed immunohistochemical and electron microscopy techniques to identify viral antigens

and virions in both circulating and tissue-associated macrophages. Furthermore, flow cytometric analyses revealed presence of MARV infection in macrophages within population of peripheral blood mononuclear cells in infected macaques (Mehedi et al. 2011). Besides this, lymph nodes, liver, and spleen exhibited most severe necrotic lesions. These organs, recognized for their profusion of reticuloendothelial cells, facilitate translocation of infected cells, resulting in spread of virus to numerous organs and establishment of a systemic infection. Other cell types susceptible to infection include hepatocytes, cells in adrenal cortex and medulla, and fibroblasts. Endothelial cells, on other hand, are targeted later in course of MARV infection in various tissues (Bente et al. 2009).

In terms of organ specificity, MARV predominantly targets liver and lymphoid tissues. Liver, in particular, serves as crucial site for MARV replication, emphasizing its significance in lifecycle of virus (Messaoudi et al. 2015). Lymphoid tissue undergoes a transformation characterized by presence of plasma cells and monocytoid cells. In vicinity of necrotic regions, basophilic bodies can be observed, either within necrotic cells or as inclusion bodies within parenchymal cells. Nonetheless, no organs remain unaffected through infection, exhibiting pathological changes characterized via focal or disseminated necrosis. Interestingly, these alterations occur in absence of significant inflammatory responses. In MVD patients, renal dysfunction commonly manifests as proteinuria (Ristanović et al. 2020). Grossly, affected kidneys display a pale, swollen appearance, indicating severe parenchymal damage accompanied by signs of tubular insufficiency (Koch et al. 2018). Microscopically, human samples reveal notable necrosis in follicles and medulla of lymph nodes, as well as in red pulp of the spleen (Geisbert et al. 2000). Additionally, there is a notable depletion of lymphocytes. In skin tissue, histopathological changes primarily involve varying degrees of dermal edema and focal hemorrhage, plus swelling and necrosis of endothelial cells (Qiu et al. 2014).

7. PATHOGENESIS

MARV infection typically occurs through unswerving touch by contaminated fluids of the body or through straight touch among unhygienic fauna or creatures. Small membrane abrasions and mucosal surfaces serve as entry points for the virus in a deceased body. Dendritic cells, monocytes, and macrophages, which are part of mononuclear phagocyte system, are untimely main cells of the MARV, as observed in various mammalian species (Alves et al. 2010). A virus has been observed in contaminated guinea pigs to replicate into macrophages prematurely twenty-four hours after infection (Ryabchikova and Price 2004). In cynomolgus macaques, infected monocytes have been detected as early as two days after exposure (Fritz et al. 2008). Macrophages and monocytes have also been acknowledged as untimely intention cells within creature models of MARV infection (Cooper et al. 2018). Cell culture studies have confirmed that individual macrophages and monocytes are extremely vulnerable to MVD because they create catching particles. Additionally, primary human endothelial cells and monocyte-derived dendritic cells (mDCs) have been shown to support MARV replication (Bosio et al. 2003). Spleen, liver, and lymph nodes are early sites of virus replication where extensive necrotic lesions are observed (Daddario-DiCaprio et al. 2006).

These appendages hold an elevated number of macrophages and monocytes (Stroher et al. 2001). It is suggested that the relocation of contaminated macrophages with monocytes keen on nearby tissues or dissemination of disease without any charge through bloodstream or lymph nodes contributes to spread of infection towards several appendages, resulting in general contagion (Schnitzler and Feldmann 2003). Extensive scrutiny has been directed towards examining free-cell viruses within tissues. Moreover, appendages of infected animals have exhibited notable signs of illness, including a significant presence within the bloodstream (Geisbert et al. 2010). In addition to dendritic cells, macrophages, and

monocytes, a wide range of cell types, including medullary cells, hepatocytes, fibroblasts, and adrenal cortical cells, are susceptible to Marburg virus infection (Yen and Basler 2016). Endothelial cells in various tissues are also targeted by a virus during MARV infection, although they are infected later in the course of disease. Involvement of endothelial cells in MARV infection and occurrence of vascular damage is still a matter of debate. Limited evidence of contaminated endothelial cells has been seen in non-human primate infections. Revolutions during the endothelium are believed to be caused by paracrine possessions of cytokines. At the delayed point of Marburg virus infectivity, viral components are inaccessible to almost all organs (Hensley et al. 2011).

Despite the presence of necrotic lesions and lofty viral consignment, minimal tenderness is monitored in affected organs and tissues, demonstrating a dysregulated resistant reaction. Significant liver pathology, characterized by elevated serum levels of liver enzymes, is commonly observed in MVD. This can lead to disruption of clotting factors and development of coagulation abnormalities (Warfield et al. 2009). A combination of these factors, along with overall disease progression and associated pathology, likely contributes to multi-organ dysfunction seen in severe cases. It is worth noting that lymphocytes are not highly susceptible to MARV infection. A hallmark of MVD is significant observation of lymphocyte apoptosis, characterized by programmed cell death of lymphocytes. However, precise molecular mechanisms underlying lymphocyte exhaustion and its role in pathogenesis of MVD are still not fully understood. Further research is needed to elucidate specific molecular pathways involved and their contribution to disease. Cytokine secretion, particularly the release of TNF-α, might cooperate with inducing apoptosis of lymphocytes in MARV infection. Infected cells are known to secrete cytokines including TNF-α which can trigger programmed cell death (Stroher et al. 2001).

8. IMMUNE RESPONSE

Indeed, understanding of innate and acquired immune responses in MARV infections is still limited. However, it has been described that MARV infection can lead to an inflammatory response characterized by uncontrolled release of chemokines and uneducable anti-inflammatory cytokines, including IL-1, 6, 8, 10, MIP-1a, and TNF-α. This excessive immune response often referred as cytokine storm that can contribute to pathogenesis of disease. Further research is needed to gain a comprehensive understanding of host immune reactions in MARV infections and their impact on disease outcomes. Expression of TNF-α and IL-6 in MARV-infected mice has been observed in a limited number of studies, and further research is needed to fully understand the immune response in animal models and its relevance to human infection (Ignatyev et al. 2000; Terajima et al. 2007; Nakayama and Saijo 2013). In vitro investigations have shown that MARV infection can induce the production of IL-6, IL-8, and TNF-α in monocytes/macrophages, indicating their involvement in activation of these immune cells (Fernando et al. 2015). Additionally, studies using tissue culture systems have demonstrated that TNF-α can increase endothelial cell permeability, suggesting its role in mediating vascular dysfunction during MARV infection (Albariño et al. 2013; Alfson et al. 2018).

During early phase of MARV infection, hematological changes such as leukopenia (reduced white blood cell count) and severe leukocytosis (increased white blood cell count) are usually observed. This can lead to significant eosinophilia (increased eosinophils), monocytosis (increased monocytes), and neutrophilia (increased neutrophils). These hematological abnormalities may contribute to immunosuppression in patients with MHF (Miraglia et al. 2019). Immunosuppression, resulting from hematological changes, can weaken the immune response and make MHF patients more susceptible to additional bacterial infections over extended sickness and healing period (Oda et al. 2016).

The specific mechanisms underlying these hematological changes in MHF patients, which contribute to immune suppression and subsequent infections, are currently being investigated. Further research is necessary to fully understand interaction between the virus, immune system, and hematological abnormalities during MARV infection. Contact between T lymphocytes and monocytes or macrophages (infected or activated) in viral infection activates Fas death receptor (Fas (CD95/APO-1) is a key member of the tumor necrosis factor receptor super family, activating apoptosis and crucially regulating the immune system) signaling pathways (Geisbert et al. 2020). Proinflammatory cytokines and nitric oxide levels increasing in blood can potentially trigger severe sepsis and apoptosis within veins. Contribution of MARV glycoprotein to lymphocyte dysfunction has not been well understood (Gross et al. 2020). Convalescent serum from patients was used to directly detect MARV antigens through immune-fluorescent-based assays during 1967 outbreaks, confirming the production of MARV-specific antibodies (Emperador et al. 2019).

9. DIAGNOSIS

Control of MVD outbreaks relies on key measures including isolation, identification, and contact tracing of infected individuals, plus laboratory diagnostics. However, clinical diagnosis of MVD in early stages of an exposure can be challenging due to presence of similar clinical symptoms to other tropical infectious diseases like malaria, rickettsia infection, and typhoid fever. This similarity in symptoms can result in significant delays in implementing appropriate infection control measures and initiating proper disease management for affected patients (Kassa 2019). It emphasizes importance of accurate and timely diagnostic techniques to distinguish MVD from other similar diseases, enabling prompt intervention and effective outbreak management. In areas experiencing an epidemic, special attention is required for diagnosis of MVD, and it is essential to consider travel history of individuals (Grolla et al. 2011). Diagnostic methods in laboratories typically include molecular, serological (serum), and virological techniques. Most appropriate method is to test blood (or serum), although fluids such as saliva (oral swab) or urine can also be used (Hartman et al. 2010).

Tissue samples obtained from autopsies can also be utilized for diagnostic purposes. In cases where blood sample is not available, breast milk can be used as an alternative specimen source (Reynolds and Marzi 2017). When dealing with suspected cases of MARV, it is advised to first contact state health department to obtain necessary permissions and guidelines for managing patients under investigation. Following guidance of state health department, specimens should be transferred directly to CDC and take preventive measures during testing. It is advised to perform these tests in the BSL-4 lab, which ensures highest level of containment and safety precautions (Racsa et al. 2013). Primary diagnostic techniques used for identification of viral genome in MVD may include reverse transcription PCR (RT-PCR) or Enzyme-linked immune-sorbent assay (ELISA) for antigen detection (Park et al. 2016). Additional methods include serum neutralization tests, electronic microscopy, and immune-histochemistry. Electron microscopy and virus isolation are also used for confirmation of virus (Brauburger et al. 2012).

ELISA serves as an alternative and confirmatory test for diagnosing MHF by detecting the antigens. This assay utilizes serum or viral protein-specific antibodies to bind to antigens (Towner et al. 2009). The IgM ELISA is mainly used to identify viral antibodies during early days of symptom onset, disappearing after infection occurs within 31 to 169 days. In contrast, IgG antibodies have been present in blood for many years (Keshwara et al. 2019). Therefore, IgM ELISA is primarily utilized for diagnosis of acute infection, but IgG ELISA is used to determine whether an individual has recovered from MHF infections or not (Sannathimmappa et al. 2021).

10. TREATMENT AND VACCINATION

Currently, no specific treatments are available for MVD. Supportive care, including fluids and symptom management, is primary approach. Experimental treatments, such as transfer of antibodies, interferon treatment, and cytokine inhibition, have shown promising results in animal models but require further research (Bausch et al. 2003). Use of recombinant nematode coagulant protein 2 (rNAPc2) in NHP models as treatment for MARV infection has not been successful. Even when administered within 30 to 60 minutes after MARV infection treatment did not provide adequate protection (Geisbert et al. 2013). Alternative treatment approaches are being explored, but there is currently no effective treatment specifically for MVD. To block the viral protein expression, some treatments are used in MRV-infected animals, specifically phosphorodiamidate morpholino-oligomers (PMO). However, the efficacy of this approach in NHP models is yet to be determined and it is important to note that these therapies are used in controlled laboratory settings, and their effectiveness may vary in real-world scenarios (Nozakiand Abou-Fayssal 2010).

To prevent MARV outbreaks resulting from laboratory accidents, strict safety measures and protocols are implemented to minimize the risk of exposure and ensure safe handling of virus. A vaccine or treatment for MVD has not yet approved, however, certain preventive measures have been implemented. These measures primarily focus on maintaining electrolyte and fluid balance, regulating blood pressure and oxygen levels, and providing blood and clotting factor replacements, which are often disrupted by infection. In cases where the disease moved forward to a modern design or combination of therapies, this was emphasized as an effective approach (Ye et al. 2023). For example, a combination of two drugs, antiviral medications and a candidate MARV-specific monoclonal antibody (mAB) has shown increased effectiveness (Hickman et al. 2022). However, further advancements are needed to improve the efficiency of herbal remedies, metabolites related to plants having immune-elevating properties, nutrition-rich foods, phytochemicals, and nutraceuticals. These include development of new chemical ligands, antiviral drugs, and broad counterpoise antibodies that can effectively treat MVD (Zhang et al. 2018).

11. DISEASE PREVENTION AND CONTROL

In absence of a licensed vaccine or widely available therapy for MVD, efforts to control infection have been challenging. In non-epidemic countries, isolated cases of MVD have been reported due to factors like infected animals or tourists spreading filovirus (Nyakarahuka et al. 2017). It is crucial to avoid spread of these viruses, and controlling outbreaks has become increasingly difficult in affected regions (Green 2012). In the past, control of MVD infection involved the collaborative efforts of various medical departments and organizations, including WHO and the CDC (Pittalis et al. 2009). Primary and secondary modes of transmission of MVD are crucial factors to address when controlling outbreaks. By focusing on interrupting transmission chain, as through isolation of infected individuals and providing proper care, it is possible to control spread of disease. Effective infection control measures and prompt response can contribute to managing and containing MVD outbreaks (Harris 2023).

Nosocomial infections, which occur within healthcare settings, have been a significant concern in spread of MVD. However, advancements in preventive medicine and increased education of healthcare workers have helped limited transmission of disease in recent epidemics. Epidemiological surveillance helps to understand outbreak's magnitude and identify transmission patterns. In disaster areas, secondary infections often arise when caring for sick or coming into close contact with the deceased during funeral rites. It is essential to implement appropriate burial and disinfection methods as well as develop plans to

prevent the spread of disease within affected region. Educating local communities about preventive measures and safe practices is important for controlling transmission of MVD. By promoting awareness and providing guidance, risk of further spread can be mitigated. Bio-security and epidemiological efforts are not enough to control outbreaks, highlighting the need for additional psychological support in affected communities (Roddy et al. 2007).

12. CONCLUSION

Since the initial case in 1967 involving contact with wildlife, there have been multiple outbreaks of MARV. Despite numerous attempts at treatment, achieving success has remained elusive. An enhanced comprehension of the clinical trajectory and pathology of MVD could yield improvements in patient care and lead to a reduction in mortality rates. The evolution of disease diagnosis has resulted in more refined test accuracies. Ongoing research efforts into diverse treatment modalities and vaccines are aimed at effectively addressing the challenges posed by this formidable virus. While certain compounds and vaccines offer partial mitigation for MVD, a comprehensive understanding of the precise pathogenesis of MARV infection following contact with reservoir animals is essential. Equally vital is unraveling the mechanisms underlying the development of asymptomatic infections. An augmented number of clinical trials are imperative for securing Food and Drug Administration (FDA) approval for treatments and vaccinations. Globally collaborative efforts involving experts from various disciplines are paramount in bolstering preparedness for MVD and in mitigating potential global health threats.

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