DOI: https://doi.org/10.54393/pbmj.v6i12.982

PAKISTAN BIOMEDICAL JOURNAL

https://www.pakistanbmj.com/journal/index.php/pbmj/index

Volume 6, Issue 12 (December 2023)

Review Article

Monkey Pox: An Emerging Outbreak

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ARTICLE INFO

Key Words:
Monkeypox Virus, Zoonotic Diseases, JYNNEOSTM Vaccine

How to Cite:
Saeed, H. A., Perveen, A., Haidar, A., Fatima, H. R., Atique, R., Aslam, M., Naveed, A., Sharif, J., & Samad, A. (2023). Monkey Pox: An Emerging Outbreak : Monkey Pox: An Emerging Outbreak . Pakistan BioMedical Journal, 6(12). https://doi.org/10.54393/pbmj.v6i12.982

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Received Date: 2nd December, 2023
Acceptance Date: 22nd December, 2023
Published Date: 31st December, 2023

ABSTRACT

Monkeypox is a viral disease, with very rare cases. It has gained attention because of its similarities to smallpox. It was diagnosed in 1958 for the first time in monkeys and then later this disease effected people of Africa who were living in the western and central parts of Africa. The virus is liable for monkeypox, an orthopoxvirus, and is generally transmitted to people through contact with animals such as rodents, monkeys, and different wildlife. Human-to-human transmission can occur, mainly in localized outbreaks. Although monkeypox is sporadic and typically considered a zoonotic disease, it has caused epidemics in Central and West Africa. These outbreaks are often connected to close touch with infected animals, especially in rural communities. Some common symptoms include rash, fever, and pustules. While the mortality rate of this disease is 1-10% which is less than small pox. Treatment includes addressing signs such as fever, pain, and skin lesions. Patients may also require hospitalization, especially if they develop extreme complications, and have to be isolated to prevent human-to-human transmission. Research into antiviral medicinal drugs and vaccines is ongoing; however, in September 2021, no licensed monkeypox-specific antiviral drugs or vaccines were available. Preventing monkeypox generally includes decreasing the risk of exposure to the virus. Key preventive measures include people in endemic regions reducing contact with animals that carry the virus, including rodents and monkeys. This review provides an overview of monkeypox, focusing on its epidemiology, treatment, and prevention strategies.

INTRODUCTION

The initial identification of the Monkeypox virus occurred in Copenhagen in 1958, when two cases of smallpox-like infection were reported among the cynomolgus monkey population [1]. The zoonotic disease monkeypox primarily impacts the Central and Western regions of Africa [2]. Although human transmission is limited, it is still possible for many factors to contribute to its occurrence. With the exception of the absence of zoonotic introductions, human infections will terminate. The virus was given this moniker because of its similarity to the poxvirus. Multiple instances of monkeypox were documented in the Netherlands and the United States between 1960 and 1968. The first documented case of human-to-human transmission of monkeypox occurred in Africa in 1970. The incident transpired in a 9-month-old male neonate who developed a rash and fever. There were no clinical symptoms observed during the initial stages of the condition. Monkeypox is categorised as an orthopoxvirus, a category that also comprises variola, vaccinia, camelpox, and cowpox. At the present time, the Orthopoxvirus genus comprises ten species, including variola (commonly known as smallpox) and monkeypox. MPXV is a DNA virus that completes its entire life cycle within the cytoplasm of the cells that are infected [3]. Smallpox and human monkeypox are zoonotic viruses that are similar in nature. The infection is transmitted to humans via direct contact with infected

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animals. Additionally, transmission via direct contact, encompassing sexual and respiratory routes, linens, and bedding, is a possibility. The recent emergence of monkeypox has been formally designated by the World Health Organisation (WHO) as a global public health emergency. Monkeypox is transmitted by a virus classified within the pox-viridae family, which is distinguished by its large size, complex morphology, enveloped structure, and linear double-stranded DNA. Lymphadenopathy, headache, lethargy, and fever are among the initial clinical manifestations of monkeypox. The facial region exhibits a greater prevalence of the rash compared to the thorax. The specimen is in a state of isolation from other species, and the precise host remains unidentified. As of May 25, 2023, a total of 250 documented cases of monkeypox have been reported across the globe. The disease manifests symptoms that endure for a period of 2-4 weeks, with a case fatality ratio varying between 3% and 6%. Approval for the use of a novel antiviral medication, which is specifically formulated to combat smallpox, has been granted in the United States. Vaccines against smallpox also provide protection against monkeypox. The concentration of cutaneous lesions influences both the severity of symptoms and the duration of the disease. The condition exhibits a heightened severity in children and expectant individuals. Several investigations conducted in Africa have established that the transmission of the disease occurs through direct contact between an afflicted person and an animal. Hunting, slaughtering, or consuming wildlife have also been identified as potential vectors of infection. Consideration was given to the genetic evolution of the virus prior to the current pandemic. Epidemics continue to be induced by it in both Central and West Africa. Over the past two decades, there have been documented cases of monkeypox among individuals who have been exposed to the disease in regions where it is prevalent. A minimum of two incidents pertaining to travel occurred within the borders of the United States in 2021. Despite the fact that monkeypox is capable of infecting a wide variety of mammalian species, it has been observed in squirrels only once. Uncertain is the extent of viral dissemination within animal populations. In some regions, the management of human monkeypox is challenging on account of insufficient resources, inadequate infrastructure, a scarcity of diagnostic specimens, and clinical complexities associated with the identification of the viral infection. Two distinct species of this virus are identified, with one species being native to West Africa and the other to Central Africa. The rash generally develops in the oral cavity before subsequently disseminating centrifugally to the face. At present, two vaccines are available for administration: ACAM2000®, which contains a live vaccinia virus that is replication competent, and JYNNEOS TM, which contains a live vaccinia virus that is replication incompetent. Mitochondrial proliferation of monkeypox may result from a compromised immune system. The aforementioned pathogen demonstrates resistance to extreme temperatures [4]. A multitude of serological assays have been utilised in order to identify and define this covid-19 virus. The CF test is considered unnecessary due to the observation of anticomplementary activity in macaque sera [5]. Primary and secondary cell lines derived from a variety of species have been shown to significantly affect the metabolism of this virus [6]. Seven to fourteen days is the incubation period for the disease in rhesus primates. The biochemical analysis yielded findings that suggested an increased urea nitrogen concentration, elevated white blood cell count, and elevated albumin levels in the blood. Changing land use, deforestation, and human expansion into natural areas are factors that have the potential to induce ecological disruptions. Enhanced interactions between human populations and wild woodland species will ensue as a consequence, thereby augmenting the potential for zoonotic spillover. When smallpox immunisations were initially suspended, only the most recent family members remained unvaccinated. At present, entire families are exceedingly susceptible, thereby creating a substantial opportunity for additional transmission among members of the same family [7]. A growing population in the Democratic Republic of the Congo (DRC) is resorting to bush meat as their main source of sustenance and seeking refuge in the rainforest, which has led to a significant public health concern regarding the prevalence of monkeypox. Declining population immunity, substandard living conditions, destitution, insufficient healthcare infrastructure, and low levels of education exacerbate the problem. The prevalence of the virus beyond Africa is demonstrated by the outbreak in the United States [8]. However, its potential impact may be mitigated in regions equipped with advanced healthcare infrastructure. Vaccination against smallpox, which comprises live vaccinia virus, is not advised as a substitute due to the potential danger it presents to members of the population with compromised immune systems and atopic conditions [9]. Due to the existence of an animal reservoir for monkeypox, eradication of the disease is highly improbable, notwithstanding the advancements in modern vaccine technology. By implementing a comprehensive strategy, the prevalence of human monkeypox infection in regions where it is prevalent can be diminished. This approach comprises two primary elements: (a) dissemination of information through educational campaigns that advocate for appropriate handling of animal reservoir species in order to avert human-to-animal

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transmission; and (b) application of barrier nursing practises and isolation of patients exhibiting acute inflammation to further impede human-to-human transmission. Without a doubt, the present circumstances necessitate heightened scrutiny and expeditious decision-making.

SYMPTOMS

The presence of various nonspecific symptoms in MPX can pose a difficulty in differentiating it from a number of other medical conditions. Several conditions that may be included in a differential diagnosis are water warts, red measles, rickettsia diseases, staphylococcus skin infections, bacillus anthracis, itch mites, syphilis, and non-infectious causes such as drug reactions that can result in rashes, as illustrated in figure 1 [10]. Chickenpox bears a striking resemblance to MPX in terms of clinical presentation. Despite exhibiting milder symptoms in comparison to smallpox, MPX remains a potentially lethal illness, boasting a 10% mortality rate that is subject to variation. In most cases, fatalities occur within the second week following the onset of the infection. Young adults and children are at an increased risk, and individuals with compromised immune systems may develop a severe form of the illness. MPX has the potential to induce a range of adverse effects, such as co-infections, respiratory complications, encephalitis, blinding keratitis, and gastrointestinal manifestations including vomiting and diarrhoea [11]. MPXV exhibits an incubation period that ranges from five days to three weeks, during which the symptoms endure for an estimated duration of two to five weeks. The initial symptoms including chills, headaches, vertigo, back pain, and muscle discomfort are non-specific [12]. Five days after the onset of fever, an assortment of lesions of varying in size manifest. Typically, they manifest initially on the face, subsequently spreading to the trunk, extremities, and even the palms and soles of the feet [13]. Some of these skin lesions attain a diameter of approximately 0.5 cm, whereas others have the potential to expand to a maximum of 1 cm. These blemishes manifest in a sequential manner, culminating in the formation of crusts that gradually detach during the healing process. Co-infections of the lesions that recur are frequent and can substantially contribute to the development of permanent skin scarring(figure 1)[14].

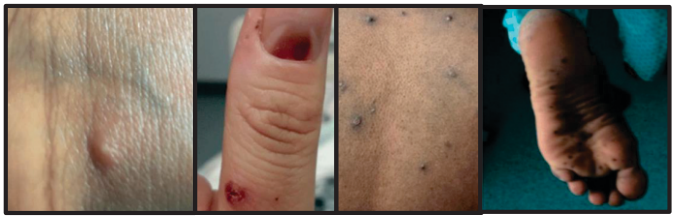

Figure 1 : Symptoms of Monkey Pox

DIAGNOSIS

An essential factor in the management of natural monkeypox infections and the timely identification of possible bioterrorism episodes is the establishment of a conclusive diagnosis [15]. Despite their similar clinical signs, it is crucial to differentiate between monkeypox, chickenpox, and smallpox [16]. Orf and bovine stomatitis are two conditions caused by parapoxviruses that can result in skin lesions similar to those observed in the US monkeypox outbreak. However, the use of electron microscopy can readily distinguish them from orthopoxviruses. Upon identification of the causal agent, the most efficient public health strategies are implementing quarantine and promptly administering ring vaccination [17]. Regrettably, there is currently no authorised antiviral treatment available for monkeypox. Due to its high transmissibility via direct touch and aerosol particles, it is imperative to handle specimens such as scabs or other cutaneous tissues cautiously, employing respiratory precautions during collection. Various laboratory diagnostic techniques are utilised to identify monkeypox, such as virus isolation, PCR, IgM and IgG ELISA, immunofluorescent antibody assay, and histopathologic examination [18]. Nevertheless, these techniques frequently lack precision and are unable to differentiate monkeypox virus (MPXV) infection from other types of poxviruses. For example, the histological characteristics of monkeypox lesions resemble those of other viral skin rashes. However, the utilisation of immunohistochemistry with antibodies specifically targeting orthopoxviruses enables the distinction between illnesses caused by herpes viruses and poxviruses. Historically, electron microscopy has been essential in viral diagnosis and can be a key method for diagnosing poxvirus infections [19]. The characteristic poxvirus virions can be visualised, displaying a unique brick-like shape and specialised structures. Electron microscopy revealed the presence of both mature and immature virions within the cytoplasm of keratinocytes during a recent monkeypox outbreak in the US. The ultimate method for identifying MPXV is virus isolation, which entails cultivating the virus in mammalian cell culture, employing PCR techniques, and subsequently conducting genetic analysis. Real-time PCR techniques that target genes specific to panorthopoxvirus or MPXV have become increasingly accessible [20]. Furthermore, a DNA oligonucleotide microarray containing the TNF receptor gene crmB has been created to quickly identify orthopoxviruses specific to certain species.

DOI: https://doi.org/10.54393/pbmj.v6i12.982

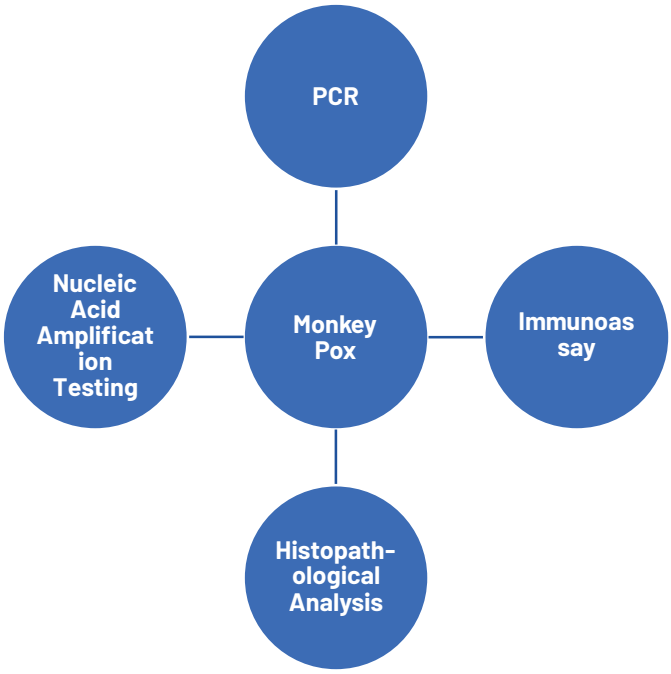

Figure 2 : Analysis Methods for Monkeypox Virus

PATHOPHYSIOLOGY

When MPV comes into contact with the human body, it can be transmitted through various routes such as intradermal, mucosa, oropharynx, and nasopharynx. After replication, in the time period of 6-13 days, the virus enters the bloodstream this condition is known as viremia. After entering the body, the virus spreads in the whole body via blood. It can affect the immune system in negative way [21]. Although the precise tissue tropism of MPV in humans remains unclear, important information has been obtained from various animal models. MPV antigens have been found in many tissues of immunocompromised mice, such as lung, liver, heart, brain, kidney, ovary and pancreatic tissue. The cynomolgus monkey also showed bacterial accumulation in specific tissues, including the salivary epithelium, fat and hair follicles of the lips, and lymphoid tissues. These data indicate that MPV has a broad tropism, making it difficult to identify the tissue that is the primary source of infection [22]. MPV is structurally and functionally similar to other orthopoxviruses (OPVs). The structure is surrounded by an outer lipoprotein membrane with a wave-like structure that provides protection to the central region containing double-stranded DNA, transcription factors and enzymes. The core part of the genome contains conserved genes that are responsible for critical housekeeping processes, whereas the terminal region of the genome contains less conserved genes that are involved in virus host interactions and virulence. MPV, a DNA virus, undergoes replication, assembly, and maturation in the cytoplasm of the host cell. The life cycle of MPV remains incompletely elucidated, however it is probable that it exhibits numerous similarities with Vaccinia virus (VACV), which is another OPV [23]. Both Vaccinia virus (VACV) and Monkeypox virus (MPV) generate two distinct forms of infectious particles: intracellular mature virus (IMV) and extracellulare enveloped virus (EEV) [24]. Intracellular mature virions (IMVs) enter host cells by the process of macropinocytosis, whereas extracellular enveloped virions (EEVs) enter by means of membrane fusion. Infectious intracellular mature virions (IMVs) are common and play an important role in the transmission of disease from one host to another. On the other hand, extracellular enveloped virus (EEV) usually moves between different tissues through body fluids and participates in the infection of the host. Although these products are generally used for OPVs, certain brands may have special features. Many OPVs, such as antibodies, evade the immune response by downregulating MHC molecules on cells that recognize the antigen. MPV, on the other hand, has demonstrated the ability to suppress T cell responses against different pathogens by attacking CD3. Genomic instability and genetic diversity influence the evolution of MPXV strains, which are DNA viruses compared to RNA viruses such as HIV or SARS-CoV-2 [25]. Recent research on the 2022 MPXV outbreak may indicate that the virus has evolved further, which may indicate that the virus has adapted to spread more quickly. In particular, isolates of this phenomenon have 40 mutations that differ from the closest species. The emergence of multiple adaptations of MPXV to infect humans could have global implications. Although some mutations can improve the disease, other mutations can be harmful, and some can provide an advantage in interaction with other species. The possibility of small genetic modifications that support the immune system is especially important for diseases with high epidemic rates. The ability of MPXV to affect the immune system is related to the homologues it encodes for animal cytokine and chemokine receptors [26]. Antibiotics can suppress the host's immune system and significantly impact infection. Although both species can enhance the quality of the virus and contribute to its transmission to humans, the relationship between the virus and the host can be characterized by stability and lack of change [27].

TREATMENT & CONTROL

Tecovirimat (ST-246) is an antiviral drug approved by the US Food and Drug Administration (FDA) specifically for treating smallpox. This drug specifically targets orthopoxviruses and is ineffective against other double-stranded DNA viruses [28]. The main focus is on a virus called palmitoylated phospholipase F13 or p37, which is found in the viral envelope and membrane. F13 is thought to play an important role in the production of extracellular

DOI: https://doi.org/10.54393/pbmj.v6i12.982

enveloped viruses (EVVs) and is important in viral entry into distant tissues, cell-to-cell transmission, and blood-borne transmission [29]. A recent study included 41 volunteers who received tecovimab at a dose of 600 mg twice daily for two weeks. All people benefited, with the most common side effects being fatigue, headache, and nausea. Additionally, a group of individuals also suffer from transaminitis [30]. Additionally, clinical studies have been conducted in treatment-naïve individuals to evaluate the safety and pharmacokinetics of tecovirimat [31]. BCV is a bioavailable acyclic lipid nucleoside phosphonate that is a lipid conjugate of cidofovir. BCV has the advantage of cidofovir because it has fewer side effects, particularly the nephrotoxicity observed in animals and humans treated with intravenous (IV) cidofovir [32]. BCV exhibits potent antiviral activity against many DNA viruses, especially poxviruses such as MPXV. A study in three MPX patients showed a significant reduction in bacterial infections after taking 200 mg of BCV per week. However, the treatment is inadequate because the liver enzyme level increases without any significant change in the patient's blood composition. A clinical study was conducted to evaluate the safety of brcidofovir (BCV) against orthopoxviruses in healthy adults. The results showed that BCV was safe and well tolerated, with no serious or life-threatening complications [33]. Additionally, a phase II clinical trial (NCT04706923) is currently evaluating the effectiveness of intravenous (IV) BCV in patients with adenovirus infection. It should be emphasized that further clinical trials are needed to evaluate the efficacy and safety of BCV in the context of MPX [34].

Vaccination

In the United States, two specific vaccines, JYNNEOSTM and ACAM200, are given to patients at risk of exposure to orthopoxviruses. This vaccine is given as a preventive measure and is often called PrEP (pre-exposure prophylaxis). People eligible for PrEP include those working in research facilities, laboratories, and public health and healthcare services. JYNNEOSTM vaccine is an unavailable vaccine based on the modified Ankara vaccine (MVA). Approved by the US Food and Drug Administration (USFDA) for use in US adults in 2019 [35]. Research has shown that it is highly effective, providing a protection rate of around 85% against MPX. The administration of this vaccine involves two doses, with each dosage being 0.5 mL in volume. These doses are given four weeks apart using subcutaneous injections [36]. In addition, they have partnered with the United States of America to develop a freeze-dried variant called MVA-BN® freeze-dried, which has successfully undergone phase 3 clinical testing. Curiously, this vaccination is referred to have distinct designations in several nations [37]. Within the European Union, this product is referred to as Imvanex, whereas in Canada, it is known as Imvamune.The ACAM2000 smallpox vaccine is manufactured utilising live vaccinia virus obtained from the New York City Board of Health in the United States. Emergent BioSolutions collaborated with USCDC [38] to create it. Initially developed as a means of preventing smallpox, it also demonstrates effectiveness in providing protection against monkeypox (MPX). Dryvax is renowned for providing immunogenic protection to around 95% of individuals who take it, albeit with adverse effects that impact around 1% to 2% of recipients. In 2008, ACAM2000 replaced Dryvax in the national strategic stockpile. Unfortunately, the production of Dryvax has been discontinued [38].

Control

The control model for managing monkeypox involves the integration of four time-dependent control factors: implementing strategies to prevent transmission from rodents to humans, reducing human-to-human contact, isolating infected individuals through contact tracing, and providing treatment to isolated individuals. Most researchers have demonstrated the effectiveness of preventive interventions in controlling infectious diseases [39]. Centres for Disease Control and Prevention (CDC) 2022 also recommended these interventions to curb the spread of monkeypox, especially during ongoing insurgencies [40]. This approach successfully prevented a significant number of individuals from getting infected.

DISCUSSION

The disparity identified between previous and recent instances of monkeypox is contingent upon the method of operation. Otherwise, all other features are rational. Recent examples have demonstrated that sexual transmission can serve as a vector for monkeypox, in addition to other mechanisms of infection. The presence of granules in the genital organs has primarily been seen in homosexual and bisexual individuals. The death rate for persons who are not vaccinated exceeds 10%, as determined by calculations. Recent study has demonstrated that administering the vaccinia vaccine also diminishes the intensity of monkeypox infection. However, vaccination was halted once the disease was eliminated, resulting in the re-emergence of human monkeypox cases in Africa and non-endemic nations. Monkeypox cases usually occur in remote locations with forests, where access to health services is generally limited. Providing medical support and treatment for problems such as eye and secondary infections, respiratory involvement, and fluid imbalance can be difficult due to restrictions in assistance and specialized care. The increase in documented instances of monkeypox in African nations that have not experienced such cases in many years, in

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addition to the diverse factors that affect the transmission of monkeypox, highlights the need to improve our comprehension of the illness and strengthen our preparedness endeavours. The World Health Organisation (WHO) and the Centres for Disease Control and Prevention (CDC) are working together on various important projects to fill knowledge gaps and develop specialized knowledge in areas where the disease is prevalent. These programs aim to enhance our understanding of the transmission of the virus, encompassing both zoonotic transmission (from animals to humans) and human-to-human transmission.

CONCLUSIONS

This epidemic exemplifies the potential of a disease that is limited to one region of the world to influence other areas significantly. Raising awareness and providing education, particularly to individuals, can contribute to the prevention and control of the disease. In order to prevent the spread of MPXV to humans, it is necessary for future research to focus on sequencing all sequenced CAR isolates and identifying all unidentified animal hosts. This will help assess the behavioural and ecological risk factors associated with human infections. Maintaining a global focus on efforts to control and prevent the disease and its transmission is crucial, since it not only endangers the affected regions but also poses a threat to international public health. Collaborative research and global cooperation are essential for increasing awareness and combating Monkeypox. In order to minimize the possible impact of this increasing infectious disease and safeguard world health, it is essential to maintain constant monitoring and be well-prepared.

Authors Contribution

Conceptualization: HAS, MA, AN, JS
Writing-review and editing: AP, AH, HRF, RA, AS
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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