Review Article

Human Monkeypox Virus (hMPXV) Remerges - Another Global Health Concern during the COVID-19 Disaster

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ABSTRACT

The increase in human monkeypox virus (hMPXV) cases amidst the COVID-19 pandemic has raised fear among the general public. The monkeypox virus and the now-extinct smallpox virus belong to the orthopox family of viruses. Although first discovered in 1958, Monkeypox was only well recognized outside the sub-Saharan African countries until the world experienced a monkeypox pandemic in May 2022. The virus is common in some areas of Africa and is often spread through close contact with an infected person or animal. However, recent international trade, travel, and tourism developments have caused viral outbreaks outside Africa. The most recent pandemic in 2022 has been strange because epidemiologists have not found a link between cases and the virus's ability to spread through sexual contact. The structural and pathogenic activities of the virus that attack host cells need to be better understood. Because of this, it is important to know how viruses and the immune system work together to develop effective ways to treat and prevent diseases.

To summarize existing research on Monkeypox, we conducted a narrative review using the MEDLINE, EMBASE, PUBMED, and Scopus databases to look at simultaneous zoonotic pandemics caused by the SARS-CoV-2 or COVID-19 coronavirus and presented the most to date information on the symptoms, epidemiology, diagnosis, prevention, and treatment of Monkeypox. However, more research on epidemiological details, ecology, and virus biology in endemic areas is required to understand the virus better and prevent further human infection. This short review discusses the research results that have already been published about how the monkeypox virus affects humans.

Keywords: COVID-19, pandemic infection, virology, sexual transmission, hMPXV

INTRODUCTION

Amid the COVID-19 pandemic, the recent worldwide monkeypox (MPX) outbreak has sparked fears of another pandemic [1]. Several significant epidemics in recent years have occurred, including AIDS, Zika, dengue, Ebola, and West Nile. COVID-19, on the other hand, is one of the most terrifying viruses of the decade. In these pandemics, long-term neurologic consequences are frequent[1]. Good examples include post-COVID-19 complications, post-Ebola syndrome, congenital Zika syndrome, HIV-associated neurocognitive disorders, and West Nile encephalitis. The public is very concerned about these problems since they have significant socioeconomic impacts. Often these long-term complications go unnoticed because the signs are first covered up by acute systemic infection and then blamed on end-organ damage or psychological pressures caused by a pandemic[2]. In this brief review, we describe previously published research results addressing the virology of the monkeypox virus in humans.

Orthopox Overview

The orthopoxvirus genus includes the monkeypox virus (MPXV). According to Amara and Mercer (2015), it is a linear double-stranded DNA virus with a specialized route of entry that resembles apoptosis[3]. In 2022, occurrences of Monkeypox were documented in areas where it was not prevalent, sparking a global public uproar. International authorities have called for action due to health concerns[3]. The World Health Organization (WHO) received a report of a case of MPX in the U.K. on May 13 2022; the patient had previously visited Nigeria, where the zoonotic monkeypox illness is common on the continent of Africa[4]. The two major MPXV groupings are the West African clade and the Congo Basin clade. The West African clade, which has a death rate of 1% and is assumed to be the cause of the present outbreak, is the less deadly of the two clades[5]. In 2003, MPXV

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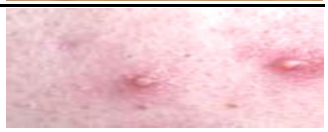
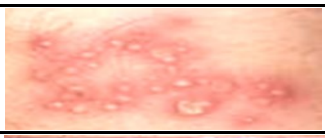
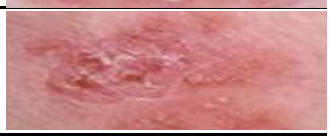
entered the United States from West Africa through a consignment of exotic animals intended to be sold as pets. It is thought that the virus from imported infected African animals subsequently infected the co-housed non-African animals like Prairie dogs[4]. These infected Prairie dogs led to the first human cases of MPX in the United States[5]. Direct or indirect contact with the infected pet prairie dogs caused 47 confirmed human MPX cases; at that time, there was no documented human-to-human transmission[6]. In addition, a significant human MPX outbreak caused by the West African lineage with around 146 clinically suspected and 42 confirmed cases were reported in Nigeria in October 2017[7]. Human MPX cases were reported in Israel (2018), the U.K. (in 2018, 2019, 2021, and 2022), Singapore (in 2019), and the United States as a result of the transfer of MPXV from Africa (2021)[5,7]. Recent bibliographic studies have published little literature on the pathophysiology, sources, and therapy of HMPXV[8]. It is dangerous because the virus is listed in the United States (Central African clade) as a select agent and classified in the European Union as a biosafety level 3 (high threat) organism[9]. The most recent developments in the virology of hMPXV are thus summarized in the current short review.

Epidemiology and Transmission

The primary route of MPXV transmission can occur in one of two ways - from animals to people or people to people[10]. Earlier epidemics were also promoted by human exposure, as documented in the 1996-1997 DRC epidemic, where 8-15% of patients reported exposure to respiratory droplets, mucosal wound exposure, or secondary infection. The transmission source was identified as fomites[10]. The past epidemics were often spread by close contact with infected animals or ingesting undercooked meat. Evidence suggests that several animals were responsible for the early spread of monkeypox[11]. However, epidemiological studies conducted in Africa found that the MPXV virus was closely related to rodents that lived in forest environments (e.g., the Gambian pouched rat, rope squirrel, tree squirrel, and dormice)[12]. Scientists did not know where it came from. Although rats were the main suspects, current MPXV outbreaks occur through human-to-human transmission, primarily sexual contact, and through respiratory droplets[13]. There is also a chance that towels, bedsheets, and sex equipment, called fomites, could spread the virus, which poses a risk to healthcare providers, the patient's family, and anyone who encounters the infectious patient[14].

Additionally, there is concern about the possible spread to domestic animals and other wild species, resulting in a potential zoonotic reservoir[15]. Seang and co-workers have reported a case of monkeypox infection in a dog from humans[16]. Recent studies have shown that infected people's sperm, saliva, urine, and faeces can all contain the Monkeypox virus[17]. Therefore, the presence of viral effusions in many body fluids suggests the potential for alternative viral

Table I: Clinical presentations of MPX with the most frequent symptoms

Stage	Stage duration	Specification	Representation
Rash	1-2 days	Multiple primary and secondary morphology lesions can lead to more extensive skin involvement.	
Macules	1-2 days	A flat lesion with a diameter of less than 1 centimetre.	
Papules	1-2 days	Elevated lesion less than one centimetre in diameter.	
Vesicles	1-2 days	Lesions less than 0.5 cm in diameter that contain fluid.	
Pustules	5-7 days	Vesicles with purulent substances, perhaps yellow or white not always contaminated.	
Scabs	7-14 days	A toughened skin layer produced during the reconstruction phase of wound healing.	

infectivity routes, which needs further investigation.

Clinical Manifestations

Clinical signs and symptoms of MPXV infections are similar to syphilis, measles, chickenpox, bacterial skin infections, itching, and drug allergies [18]. Rapid differential diagnosis is essential for preventing viral transmission in a population. The clinical presentations of MPX with the most frequent symptoms are shown in **Table I**. The clinical symptoms of the monkeypox disease resemble those of smallpox. Headache, fever, chills, sweating, dry cough, myalgia, paralysis, and lymphadenitis of the neck and inguinal nodes are all non-specific symptoms of the prodromal phase[18]. The incubation period of Monkeypox is between 12 and 21 days, and the disease has two phases[20]. There is a pre-eruptive phase (which lasts about five days) followed by an eruption (within 1-3 days of the onset of fever). Smallpox causes a high fever for the first three days. Then, a rash that looks like chickenpox appears on the face and the rest of the body, including the inside of the mouth, the vaginal area, the palms, and the soles[20] (**Figure III**).

The pathognomonic sign of Monkeypox is lymphadenopathy, which sets it apart from smallpox and other viral rash diseases like chickenpox. However, in rare circumstances, clinical symptoms alone may not differentiate these diseases[21]. In the skin eruption phase, the rash appears sequentially and develops into a macule, papule, vesicle, pustule, and crust over two to four weeks. Dehydration due to vomiting, diarrhoea, and bacterial superinfection are two possible complications in Monkeypox disease[20,21]. Sepsis, neurological impairment, and eye injury are possible outcomes. Approximately 30% of HIV patients with concurrent monkeypox infection displayed no outward pox symptoms[22]. Most people in this subgroup are well taken care of with anti-retroviral treatment, and several large groups of monkeypox patients have reported that at least 40% of them are HIV positive[23]. Co-infection has been reported with other sexually transmitted diseases, such as gonorrhea, chlamydia, and syphilis, with one cohort having 29% of concurrent sexually transmitted infections[24].

Monkeypox Diagnosis

Virus isolation and culture, real-time PCR, immunohistochemistry, fluorescence microscopy, and immunological screening, especially for new antibodies like IgG and IgM, are the ways to diagnose MPXV in lab[23]. Serology or methods based on antigens should not be used to try to make a diagnosis because they could react with other orthopoxviruses. Samples of Monkeypox should be taken from open sores on the skin with swabs made of nylon, polyester, or Dacron[25]. After the swab, the sample should be put in a clean, sterile container and stored in a refrigerator/cold freezer[26]. PCR has emerged as the gold standard among laboratory diagnostic techniques owing to its reliability and sensitivity. WHO says confirming an MPXV infection requires nucleic acid amplification testing (NAAT) using real-time or traditional PCR to find the viral DNA sequences. MPX can be diagnosed by PCR alone or in combination with sequencing[27]. **Table II** lists the primers and probes used in PANPOX-real-time PCR[28,29]. Recent studies show that T-cell responses and antiviral antibodies are increased during infection; discovering novel effective serological approaches might enhance MPX detection throughout outbreaks[30]. The rapid screening test Tetracore Orthopox Biothreat Alert®, based on lateral flow, can be used during high-priority scenarios to test for hMPXV[31]. Flow-through antigen capture ELISA has also been employed to build a more sensitive diagnostic tool. The virus's G2R gene can be copied in less than seven minutes with a new test called rapid recombinase polymerase amplification (RPA)[32]. The assay exhibited 100% specificity and 95% sensitivity for both virus strains. More information can be accessed from the CDC and state health lab websites[33].

Table II: Real-Time PCR Primers and Probes for Diagnosis of Monkey Pox Virus

MPXV Assay	Forward primers	Reverse Primers	Probes
G2R -WA West African specific	5-CACACCGTCTCTTCCACAGA-3	5-GATACAGGTTAATTTCCACATCG-3	5-FAMAACCCGTCGTAACCAG-CAATACATTT BHQ1-3
C3L Congo basin specific	5-TGTCTACCTGGATACAGAAAGCAA-3	5-GCCATCTCCGTTTAATACATTGAT-3	5-FAMCCCATATATATGCTAAATGTAC-CGGTACCGGA-BHQ1-3
G2R-G Generic	5-GGAAAATGTAAAGACAACGAATACAG-3	5-GCTATCACATAATCTGGAAGCGTA-3	5-FAMAAGCCGTAATCTATGTTGTC-TATCGTGTCC-BHQ1-3
RT-PCR Primers PANPOX	5- CCDCAYCARYTVGCIACIBTIGAYT-3	R 1: 5 GMDATIAYIGTYTTICCTGAICCCAT-3 R2: 5-GCCACGAATGTCTTACCACTTCCCAT-3	A:5-FAMWYRTGAAAYAWYADDRCDST-MGB-3 E:5-FAMTYATGAAAYADYAWNRCWYT-MGB-3 C:5-FAM-ATRTGRAAHARYARHACRCTYYTRT-MGB-3 hGC:5-FAM-ATGTGTGRAASAGVARSAYRTC-MGB-3

Treatment

Even though several potential antiviral drugs have shown effectiveness against MPXV invitro and invivo models, none have been tested so far in controlled clinical studies [35]. Monkeypox is not currently known to have any specific therapy. The main guidelines for treating an MPXV infection are supportive therapy, controlling symptoms, and treating bacterial infections simultaneously.

Antiviral drugs

Antiviral drugs, including cidofovir, brincidofovir, and tecovirimat, are effective against MPXV based on treatment results for smallpox[36]. Tecovirimat inhibits viral outflow from infected cells by inhibiting the viral envelope protein p37. In case of a pandemic, the CDC has created the Extended Access Investigational New Drug (EA-IND) protocol, which allows tecovirimat, cidofovir, and VIGIV to be taken out of the Strategic National Stockpile to treat the confirmed OPX virus infections[37]. In vitro screening of 132 clinically approved drugs showed atovaquone, mollupiravir, and mefloquine to be effective against MPXV[38].

Vaccines

Currently, two vaccines in the United States are authorized to protect against smallpox and Monkeypox. One vaccine, JYNNEOS™, uses a live, attenuated form of the vaccinia virus that can cause a robust immune response, even though it cannot multiply in the body[39]. Other Vaccine, ACAM2000®, a live attenuated vaccine, should be used cautiously as it can transmit the virus to individuals who have not been previously immunized; In addition to protecting against severe monkeypox disease in nonhuman primates, LC16m8 vaccination was developed to reduce viral replication[40]. CDC also recommends using an investigational vaccine called Aventis Pasteur Smallpox Vaccine (APSV) during emergencies[41]. Global public health organizations place a high premium on preventing infectious disease epidemics, and infected countries should implement a widespread vaccination campaign using the vaccinia vaccine.

Mysterious 2022 outbreak in India

Scientists and health officials were concerned about how the virus spread from person to person when thousands of MPXV cases were reported in non-endemic areas in 2022. As of October 18 2022, 29 countries across the EU/EEA have reported 20,544 confirmed monkeypox (MPX) cases worldwide. So far, Turkey and three western Balkan countries have reported 63 cases. More cases have been reported since the start of the pandemic in Spain (7239), France (4084), Germany (3651), Netherlands (1,226), and Portugal (920). The three countries with the highest overall notification rates are Spain, Portugal, and Luxembourg. 2022 recorded a worldwide monkeypox epidemic without any well-known epidemiological links to central or western Africa. Using the sequence analysis, the MPXV clade three viruses (which used to be a subset of the West African clade) were found to be the cause[28]. Transmission of the disease was highest among males who had intercourse with other men, suggesting that male-to-male sexual contact may be a factor in the spread of the current pandemic[29-31]. Current events are fascinating to watch and monitor as they evolve due to the genomic structure of the virus, which does not undergo significant changes (as opposed to COVID-19).

The first two MPXV cases in India, imported from the United Arab Emirates (UAE) in July 2022, have been identified and genetically characterized. The case of a 35-year-old male engineer who had travelled from the UAE to Kerala in India was confirmed on July 5, 2022; he began to develop myalgia and a low-grade fever[42]**.** After another four days, on July 8, 2022, a 31-year-old male, a second patient from inside the same state (Kerala), began to experience dysuria and genital swelling[43]. The third case was just reported from the Mallapuram district in Kerala on July 22[44]. All three male patients travelled from the UAE to India and exhibited several vesicular rashes in their mouths and lips with a single lesion on their sexual organs. The lesions varied in size from 0.5 to 0.8 cm. In the capital, New Delhi, the fourth case of MPX has been found in someone who has never been out of the country. Public Health and epidemiological organizations must detect, manage, and advise society on zoonotic spillover events as they grow more frequently due to climate change[45], species migration[46], deforestation[47], petting zoos, etc., and increased human-animal interactions.

CONCLUSION

Monkeypox is a highly infectious orthopoxvirus, currently generating a worldwide epidemic, particularly among homosexual males. The current outbreak of Monkeypox shows how the disease's spread is changing, which means strict epidemiological monitoring is needed to stop it from spreading to countries where it is not common. To prevent this pandemic from spreading worldwide, public health officials, medical professionals, and the community must work together to spread information, get the necessary diagnostic tests, do contact tracing, and ensure that infected people and those in contact with them have access to medical care. The COVID-19 pandemic was a good learning chance; those lessons will help manage and control the human monkeypox virus. Governments should adopt, acquire the ability to respond concurrently, and quickly put control measures without hesitation.

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on request. Privacy or ethical restrictions bound us from sharing the data publically.

AUTHOR CONTRIBUTIONS

Nagarajan P: Conceived the idea, designed and written the article
Sivanandham M: Provided constructive comments, reviewed and edited the article
Rangarajalu K: Data collection, referencing, aligning and editing the article
Howlader A: Data collection, referencing, aligning and editing the article
Louis LRP: Provided constructive comments, reviewed and edited the article

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