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Monkeypox: An emerging zoonotic pathogen

Beig M *et al.* Monkeypox review

Masoumeh Beig, Mehrdad Mohammadi, Fatemeh Nafe Monfared, Somaieh Nasereslami

Abstract

Monkeypox virus (MPXV), belonging to the orthopoxvirus genus, caused zoonotic viral disease. This review discusses the biology, epidemiology, and evolution of MPXV infection, with particular reference to cellular, human, and viral factors, virus transmission dynamics, infection, and persistence in nature. This review also describes the role of recombination, loss of the gene, and gene gain in MPXV evolution and the role of signal transduction in MPXV infection, and provides an overview of the current therapeutic options access for the treatment and prevention of MPXV. Finally, this review highlighted gaps in knowledge and proposed future research endeavors to address the unresolved questions.

Key Words: Poxviridae; Orthopoxviruses; Monkeypox viruses; Epidemiology

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Core Tip: Since May 13, 2022, cases of monkeypox have been reported to World Health Organization (WHO) from 12 Member States that are not endemic to the monkeypox

virus, across three WHO regions. This emergent pathogen is a major concern in the world after severe acute respiratory syndrome coronavirus 2 and needs to epidemiological and other data from the virus. The objective of this report is to demonstrate comprehensive data in review formation.

INTRODUCTION

It is one of the human orthopox viruses (OPVs), which consist of **variola virus (VARV)**, **cowpox virus (CPXV)**, and **vaccinia virus (VACV)**^[1]. Monkeypox is similar to smallpox but is collaborated with a milder rash and diminishes mortality^[2]. This study aims to review the present awareness concerning infection biology systems, epidemiology, and the evolvement of the monkeypox virus (MPXV).

History of monkeypox virus

Monkeypox was first detected in 1958 when two smallpox-like diseases broke out in monkey colonies kept for research^[3]; therefore, the name monkeypox and the first human case of the virus were registered in 1970 in the Democratic Republic of the Congo^[4]. Amplified attempts to destroy MPXV have since been documented in humans in other Central and West African countries^[5].

Morphology, genome organization, and morphogenesis

The MPXV virions morphology are brick-shaped or ovoid particles^[6]. Membrane bonds, impenetrably compressed core including enzymes, the transcription factors, and a double-stranded DNA genome, sheltered by the outer membrane^[7,8]. Its genome includes linear double-stranded DNA (≈ 197 kb), although its entire life cycle occurs in the cytoplasm of infected cells. The genome encodes all the proteins required for viral DNA replication, transcription, virion assembly, and egress nome^[6,9]. Two infectious viruses are produced within poxvirus-infected cells: intracellular mature virus and extracellular enveloped virus^[10,11] (Figure 1).

INFECTION BIOLOGY, DIAGNOSIS, AND TREATMENT

Animal models

A perfect brute mannequin because of reading ethnic disease use a path about contamination so mimics the herbal transmission on the pathogen or exhibits progression, morbidity, yet mortality comparable after ethnical infection^[12,13].

Additionally, the animal model must have one or more modes of transmission that mimic human cases^[14]. In addition, the crimson patches regarding all MPXV examined animals at the vaccination site, reduction over physique measure between close animals, or starting about epoch 14 since the challenge, a continuous increase between physique measure over complete breathing animals in the immunization agencies used to be done longevity^[15,16]. Only three of the wild-derived strains (CAST/EiJ, PERA/EiJ, and MOLF/EiJ) were highly sensitive to MPXV in a study that examined the sensitivity of 38 inbred strains of mice (32 classical inbred stresses and six wild strains), while every ace inbred lines had been anxiously strong after intranasal MPXV infection. CAST/EiJ is the just sensitive according to MPXV, along with an LD50 of 680 or 14 infectious gadgets using intranasal yet intraperitoneal infections^[2,17].

Transmission

¹² Two possible routes of MPXV transmission are animal-to-human and human-to-human transport^[18]. Droplet infection then contacts with anatomical fluids, vitiated environments, patient objects, and skin lesions regarding a contaminated character are associated with human-to-human transmission stability^[6,18]. The Congo Basin group is more virulent than the West African group and contributes more to interpersonal transport^[19]. Transmission from animals to people takes place via direct counsel and consuming the herbal viral host's stability^[20,21]. Furthermore, zoonotic transmission can show up thru direct touch, including blood, physique fluids, and the inoculation of mucocutaneous lesions on a contaminated animal. permanency^[22].

Sexual transmission of MPXV: MPXV outbreaks are not typical, as many patients are unrelated to travel to Central or West Africa and episodes of the virus in endemic areas. The monkeypox virus is currently observed ² among men who have sex with men (MSM) in the United Kingdom. In the studies conducted, a high proportion of simultaneous sexually transmitted diseases and frequent anogenital symptoms were found, which

indicates the possibility of transmission through local inoculation during close skin-to-skin or mucous contact during sexual activity [1,23,24].

Transmission by MPXV-contaminated surfaces: Although co-transmission between humans and animals was reported as the primary mechanism of disease spread in various studies, transmission to patient care personnel through surfaces contaminated with MPXV was rarely reported. Infected objects may also cause indirect transmission of the MPXV. However, there is insufficient information on the environmental contamination of surfaces with MPXV^[25].

Diagnosis methods

Phenotypic approaches: According to the clinical diagnoses, In MPXV, after a 3-wk incubation period (typically 4-21 d), a prodromal illness generally follows it with various signs including fever > 38.3 °C, back pain, myalgia, headache, intense asthenia, pharyngitis, drenching sweats, malaise and especially lymphadenopathy, occurs for a period of 3-5 d^[6,26-28]. After the prodromal stage, vesiculopustular rashes appear during the exanthema phase (with few or severe thousand lesions, synchronic or asynchronous), beginning at the face, shown within 1-10 d of development, which affects 95% of the patients^[29], followed by palms and soles (75%), oral mucosa (70%), genitalia (30%), and conjunctiva (20%). These skin lesions evolve from macules to papules, vesicles, pustules, and finally, scabs or crusts that fall^[28]. Lesions in MPXV patients appear monomorphic, pea-sized, and complex, similar to smallpox^[30]. The harvest-like appearance of the MPXV lesion, its low centrifugal spread, and among the clinical features that distinguish it from smallpox is the appearance of lymphadenopathy in MPXV^[31]. These skin manifestations compromise the skin eruption period of the disease, in which patients are contagious. Before that, patients are not able to transmit the virus. The natural history in patients without complications regularly lasts 2-4 wk^[28]. Possible detection of MPXV based on clinical signs is essential to identify suspicious cases during surveillance. Nevertheless, the clinical case

definition for MPXV based on unconfirmed studies has high sensitivity (93% to 98%) and low specificity (9% to 26%)[31,32]. According to the instance case definition, a character anybody meets the action announcement because a suspected law and one then greater concerning the according to must: hold an epidemiological link (face-to-face exposure, which includes healthcare people besides sight yet respiratory safety); direct bodily advice together with pores and skin then skin lesions, along with sexual contact; or consultation along contaminated materials, specific as like clothing, bedding then dishes, within 21 d before signs appear. Laboratory research does not validate the clinical action definition, but so does an epidemiological link, including a likely then proven case. A confirmed suit is a clinically like-minded factor hooked up between the laboratory[28].

Genetic methods: It is recommended that genetic ¹¹ techniques, including polymerase chain reaction (PCR) or real-time PCR (RT-PCR), be performed in a biosafety level 3 facility[33].

Routine detection of MPXV DNA in clinical and veterinary specimens and cell cultures infected with MPXV was performed by RT-PCR targeting conserved regions of the outer coat protein (B6R) gene, 1 DNA polymerase E, the DNA-dependent RNA polymerase subunit 18, rpo18, was targeted and the F3L genes[33,34]. Restriction fragment length polymorphism (RFLP) of genes or PCR-amplified gene fragments is also used to detect MPXV DNA, but RFLP is time-consuming and requires viral culture[35]. Additionally, since RFLP of PCR products requires enzymatic digestion after gel electrophoresis, it may not be an appropriate method in a clinical setting where the speed, sensitivity, and specificity methods are essential. Whole genome sequencing (NGS) applied sciences stay the wealth value because detecting MPXV then ignoble OPVs, but this science is expensive, then downstream sequencing records processing requires full-size computing limit permanency[36-38]. Therefore, NGS may not be a fantastic detection method, mainly in resource-poor international locations in sub-Saharan Africa. Although RT-PCR stays the method over the desire for activities

discovery of MPXV, such needs must be complemented by genome sequencing technological know-how after supplying real-time facts on the mischievous genome, which is quintessential for interventions. evidence-based epidemiology (Figure 2)^[32].

Immunological methods include utilizing enzyme-linked immunosorbent (ELISA) and immunohistochemical assays to determine IgG and IgM antibodies and detect viral antigens^[39]. Immunochemical analysis can distinguish poxvirus from herpes virus infection using polyclonal or monoclonal antibodies to all OPVs^[11]. It has been prepared that antibodies to the virus also have cellular responses and enhancements at the time of disease onset. About 5, 8 d or more after the onset of the rash, IgM and IgG are formed in the serum, respectively^[40]. Detection of IgM and IgG antibodies in unvaccinated individuals with a history of inflammation and severe illness may increase indirect MPXV discrimination. Despite this, these methods are not specific to MPX detection and can detect other types of OPVs. to illustrate^[32,41]. On the other hand, IgM can assess MPX infection in people with a history of smallpox vaccination^[42]. A positive IgM capture ELISA test indicates recent exposure to OPV (possibly MPXV in endemic areas) in vaccinated individuals. Conversely, a positive IgG capture ELISA test indicates that a person has been exposed to OPV through vaccination or natural infection. Therefore, IgM and IgG in a sample are strong evidence of recent exposure to OPV in previously vaccinated or naturally infected individuals. Thus, IgM in individuals vaccinated against smallpox in MPX-endemic regions reflects recent exposure to MPXV^[43,44].

Electron microscopy: MPXV under electron microscopy seems intracytoplasmic brick-shaped with lateral bodies than an interior bottom sure respecting 200-300 nm. Although this technique is no longer a specific prognosis due to the fact OPV kind cannot stay differentiated morphologically, that suggests so much the demonic belongs according to the poxviridae family toughness^[45].

Virus-host interaction

Host and tissue tropism: Members of the OPV family are thought to exhibit diverse spectra of host tropisms^[46]. Although the reservoir host for MPXV has not been definitively identified, many mammalian species are naturally infected with MPXV^[47]. So it is believed that MPXV has a wide host range. Previously, after the challenge with Congo Basin MPXV, large amounts of viral DNA and viable virions died in a variety of animal tissues, suggesting broad tissue tropism. The immunohistochemically and histopathological tests of Falendysz *et al*^[48] have found that the MPXV antigen is recognized in the ovarian, brain, heart, kidney, liver, pancreatic, and lung tissues; nevertheless, ovarian tissues were susceptible to MPXV^[49].

Host in the responses to the virus: PXVs develop many strategies to escape the host's immune response to infection. Natural killer (NK) cells kill virus-infected cells by secreting cytokines that stimulate other cell types, such as T cells and dendritic cells, to act moderately^[50]. MPXV infection can change lymphocyte numbers, counting NK cell changes in non-human primates (NHPs), lymphadenopathy, and lymphocyte consumption in MPXV disease of MPXV-infected NHPs. After Gavin *et al*^[51] test utilizing prairie pooches as a show, a noteworthy increment within the number of all NK subsets (CD16- CD56-, CD16+, CD56+, and CD16+ CD56+) was watched on the seventh day after vaccination. Moreover, the expression of chemokine receptors (CXCR3, CCR5, CCR6, and CCR7) on each NK cell subset recommends that word of the receptor taken after the MPXV challenge be postponed or decreased^[11,52]. Hammarlund *et al*^[53] anticipated that MPXV has a safe avoidance component such as CPXV. In any case, the avoidance instrument utilized by MPXV ensures the viral store from resistant reconnaissance by repressing the actuation of CD4+ and CD8+ T cells after interaction with MPXV-infected cells. Destitute acknowledgment of MPXV-infected monocytes by antiviral CD4+ and CD8+ shows that MPXV does not actuate the generation of provocative cytokines (IFN- γ or TNF- α) by virus-specific T cells^[52]. Antiviral T-cell responses had been substantially increased than contamination along VARV alone.

However, T-cell cytokine responses had decreased by 95% after co-infection, including MPXV and VARV, then utilizing 80% when low-dose MPXV was added (VARV: MPXV ratio regarding 10:1)^[54].

Treatment

Vaccination: The smallpox comment protects men and women from smallpox using growing redemption to smallpox. The smallpox gloss incorporates a live vaccinia virus, not a killed then thin virus^[55]. The vaccinated people must take precautions when caring because of the place regarding their weapon where she had been vaccinated to stop the vaccinia virus from spreading. Also, the vaccination is fair to smallpox demonic yet can't purpose smallpox. The smallpox comment has side results than risks^[56]. Most humans bear mild reactions such as flank pain, fever, and body aches^[51]. However, incomplete people may also reply differently, out of big after life-threatening^[57]. Although smallpox vaccination can shield human beings from smallpox for about three in imitation of 5 years, then its time, its potential to protect humans decreases, and because of long-term protection, human beings may also need assistant vaccination^[58]. Several reviews suggest that smallpox vaccination provides cross-protection against common OPV species and MPXV. All human beings beforehand vaccinated against smallpox were discovered in conformity with keeping 85% out of danger towards MPXV^[59]. The smallpox annotation (ACAM2000TM) was once advocated ⁶by the Centers because Disease Control and Prevention (CDC)^[60].

The attenuated vaccine, IMVAMUNE, is no longer accessible to the average common yet is now not back in MPXV topic areas^[61]. A third-generation modified Ankara annotation has been selected with the aid of the Food or Drug Administration (FDA) and the European Medicines Agency after stopping varicella or monkeypox in adults (age 18 years) at expanded jeopardy of VARV and MPXV infection)^[61,63]. Durability Unlike the ACAM2000 vaccine, IMVAMUNE is no longer negated because it uses humans with immunodeficiency problems, such as immunodeficiency attributes and atopic dermatitis. Neither ACAM2000 nor IMVAMUNE is elected to use the specific

population^[61,63]. Vaccination is also recommended for sexually high-risk people, including MSM, yet those with a history of sexually transmitted diseases such as ethnic immunodeficiency malevolent (HIV), syphilis, and gonorrhoea. However, so are no statistics about immunization, including a smallpox comment kind of JYNNEOS®/IMVANEX® that may confer defensive redemption in opposition to sexually transmitted MPXV^[51,63].

Antivirals: There is no approved, out-of-danger remedy because of mischievous monkeypox infection. A 4-rifluoromethylphenol spinoff and tecovirimat (ST-246 yet TPOXX®), supported by the FDA, has been clinically examined using beast models^[64]. This medicine has been shown to stay acceptable in unwell animals. According to a CDC report, ethnic clinical trials, including tecovirimat, show that although the treatment is well tolerated and safe, there are inadequate statistics on its usefulness in treating monkeypox in humans^[61,65,66]. Similarly, Vitro brute studies with cidofovir or brincidofovir (CMX001 yet hexadecyloxypropyl-cidofovir) put down the viral DNA polymerase, or the past is an acyclic nucleoside phosphate while the recent is a thin conjugate regarding cidofovir^[61,66,67]. But then, brincidofovir has increased cytotoxicity or higher antiviral undertaking than cidofovir towards VARV, MPXV, VACV, and CPXV *in vitro*.

The Brincidofovir has a higher selectivity index because such is extra than 25-fold greater brawny than cidofovir. Cidofovir is a nucleotide monophosphate analog. Another dynamic prescript below looking after against poxviruses was once NIOCH-14, a precursor regarding tecovirimat^[66-68]. Although the aptitude over NIOCH-14 towards VARV, MPXV, and ECTV is similar according to so much on tecovirimat of Vitro studies, following appropriate reasons such as much its passionate antiviral recreation in opposition to various OPVs then less complicated production than tecovirimat, has been recognized so an essential antiviral candidacy of the future. Ribavirin yet tiazofurin inhibited the duplicate concerning every the tested OPVs, together with VARV and MPXV life more sensitive than the lousy viruse^[59,61,68,69].

Saquinavir, ritonavir, and nelfinavir are protease inhibitors, or efavirenz, stavudine, yet zidovudine reverse transcriptase inhibitors have been unconscious against OPVs. At the same time, Two adenosine analogs (C-ca3-Ado then C3-Npc A) hold been shown to conformity with bear a protective faculty in opposition to OPV assayed through viral replication, or these tablets are additionally inhibitors concerning S-adenosylhomocysteine hydrolase (SAH)^[59,61,68,67]. These SAH hydrolase inhibitors had broad antiviral exercise however showed no detectable undertaking towards CPXV between vitro. Using the specific mechanisms, cidofovir yet N-(2-hydroxypropyl) methacrylamide inhibiting the viral duplicate showed recreation towards PXVs. However, adefovir or dipivoxil represented no sizeable pastime towards poxviruses.

Furthermore, adenosine oxide N1 exhibited considerable play towards OPV by inhibiting CPXV viral reproduction in vitro by blocking viral mRNA translation^[52,68,70]. Although there is no healing therapy because MPXV is managed only with supportive than evidential treatment, the trouble with this is so much that its type is solely suitable for evidentiary individuals^[68,66]. Thus, according to others, environmentally friendly MPXV vaccination and antiviral sellers are required to prevent transmission from asymptomatic people.

Biocidal agents and disinfectants: On June 5, 2022, a lesson was carried out in imitation ³ to evaluate published data about the antiviral effect of biocidal agents and disinfectants against the MPXV or lousy orthopoxviruses. At least four log₁₀ be able to inactivate vaccinia viruses into deferment experiments or ³ on artificially contaminated surfaces with 70% ethanol (70%, ≤ 1 min), peracetic sour taste (0.2%, 10 min), then probiotic cleaner (1%-10%, 1 h). The deceleration exams also confirmed as ² hydrogen peroxide (14.4%), iodine (0.04%-1%) then ³ sodium hypochlorite (0.25%-2.5%; 1 min), glutaraldehyde (2%; 10 min) yet orthophthalaldehyde (0.55%, 5 min) were effective. Artificially filthy tiers on copper (99.9%) had been equally fine towards vaccinia evil, yet MPXV at 3 min. For the inactivation over MPXVs, desire is attached to disinfectants whose efficacy statistics have been decided between suspension tests or under empirical

prerequisites along exceptional organic hundreds similar in conformity with the contract over blood, respiratory tract, or cutaneous lesions [71].

CONCLUSION

As of early May 2022, ¹⁵ cases of MPXV have been reported from countries that are not endemic to this disease and continue to be written in several endemic countries. Thus MPXV is no longer limited to the endemic regions as travelers have carried MPXV from Africa to the United States, the United Kingdom, Israel, and Singapore in recent years. As a result, MPXV is a severe reemerging pathogen with global outreach. Community transmission of the MPXV has occurred among MSM men in the United Kingdom without direct contact with people returning from endemic countries. Also, in a study, ¹ a case of a 26-year-old HIV-infected male, without a history of travel to endemic countries, with high fever (up to 39 Celsius degrees), chills, rectal pain, vesiculopustular rash, dysphagia, and skin lesions mainly in the anogenital area that developed a mild form of the disease, with ¹⁷ admitted to Hospital for Infectious and Tropical Diseases, Romania. This was ¹ the first case of MPXV confirmed in Romania, with ¹ suggestive epidemiological and clinical features. Raise awareness of MPXV transmission, especially in populations with high-risk factors, and a better understanding of how to dispatch this virus for infection control, prevention, and contact tracing are needed. ¹ Public health authorities and clinicians must consider the diagnosis of MPXV in all patients with typical rash and risky sexual behavior, in particular in those with recent sexual contact with partners who traveled to countries with reported cases of MPXV or partners with the same clinical manifestations even if they do not travel in other countries [72]. Therefore, strategies to support sexual health and other specialized services in managing this condition; also, national and global research efforts for laboratory diagnosis, infection control, and treatment strategies should be intensified. The current establishment and implementation of the Surveillance Outbreak Response Management Analysis System are required for MPXV outbreaks worldwide.

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