Review Article

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Monkeypox: An Uncommon Re-emerging Virus- Threat to Mankind

Microbiology Section

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ABSTRACT

Monkeypox Virus (MPV) causes rare zoonotic illness. The Central African (or Congo Basin) clade and the West African clade are its two genetic subgroups, of which Central African subgroup is more lethal. To distinguish between the lineages, sequencing is crucial. As it was first isolated from captive monkeys that is why it is named as MPV. Its clinical features are similar to small pox. Undiagnosed acute rash with one or more symptoms, such as headache, fever, lymphadenopathy, myalgia, back pain, or asthenia, are considered common clinical findings. Real-Time Polymerase Chain Reaction (RT-PCR) is used in the laboratory diagnosis. There are various complications of monkeypox disease that includes bacterial infection of skin, skin scarring, hyper or hypopigmentation, permanent corneal scarring (vision loss), pneumonia, dehydration, sepsis, encephalitis and death. The drug of choice includes Tecovirimat, Cidofovir, Vaccinia Immune Globulin Intravenous (VIGIV), Brincidofovir. ACAM2000, LC16m8 and modified vaccinia Ankara are few options for vaccines but still under investigation. Though the disease is self-limiting but may complicate and has morbidity as well as mortality. So, it's better to prevent the spread of the disease by early identification, contact tracing, isolation with stringent hospital infection control practices with early initiation of treatment.

Keywords: Central African clade, Cytopathic effect, Monkeypox virus, West African clade

INTRODUCTION

The World Health Organisation (WHO) declared monkeypox as "evolving danger of moderate public health concern" on 23rd June 2022, after more than 3000 MPV infections were detected in more than 50 nations across five regions since early May 2022. The MPV having double-stranded DNA causes monkeypox disease. It is also seen that smallpox vaccine proved effective against MPV. Smallpox immunisation with the vaccinia virus provided protection against MPV. Man-to-man and animal-to-man transmission are the two methods of spread. The route of transmission is by close contact with infected person and by sexual contact with infected person. The MPV, is a part of genus Orthopoxvirus (OPV), family *Poxviridae*, and subfamily Chordopoxvirinae, is the cause of the rare zoonotic disease known as monkeypox. It was initially found in a colony of captive monkey in 1958 [1]. Monkeypox is similar to smallpox and smallpox immunisation with the vaccinia virus provided over 85% protection against monkeypox [2]. As it was initially discovered in monkeys, it was given the name "monkeypox." The two genetic lineages of monkeypox are the Central African (or Congo Basin) clade and the West African clade, with the Central African subgroup being the most fatal. Sequencing helps to identify these clades as separate. In Central Africa, the case fatality rate among unvaccinated children was 11%. Patients recover in four weeks completely with the exception of scarring and skin discolouration [3]. The deletion of a portion of the genome may impact the virulence and replication potential of the virus [4]. Since 1970, 20 human cases from West and Central Africa have been reported. Electron microscopy was employed for diagnosis and isolation, while serological testing was also performed in other instances [5]. Monkey pox has several clinical characteristics similar with smallpox [6]. In addition to generating pock lesion in the Chorioallantoic Membrane (CAM) of growing embryonated chick egg, it also results in skin lesions, keratitis, and cytopathic (CPE) reactions in rabbits, mice, and mammalian cell cultures. Additionally, encephalitis is connected to it. The virus belongs to the vaccinia-variola subgroup and resembles other poxviruses in size and structure [3].

The MPV is constantly associated with places where it has been associated since long time, but various analysis about it, has been neglected and underfunded. The WHO declared monkeypox as "evolving danger of moderate public health concern" on 23rd June 2022, after more than 3000 MPV infections were detected in more than 50 nations across five regions since early May 2022 [7]. MPV is spread through large respiratory droplets, close or direct touch with skin lesions, and possibly contaminated fomites [8]. There is no conclusive proof that seminal or vaginal secretions can transmit it sexually. Foetal fatalities and vertical transmission have both been reported [9]. This review article will give information about the epidemiology, spread of MPV, and routes of transmission so that one can be aware of MPV. Vaccination against small pox is protective against MPV. MPV has similarities with smallpox. This article will brief about sample collection, processing, diagnosis and treatment.

Morphology

The MPV genome is made up of a 197 kb long linear double-stranded DNA [10]. This virus has enveloped double-stranded DNA and belongs to OPV genus of *Poxviridae* family [11,12]. Except, for the requirement for host ribosomes for mRNA translation, poxviruses have all the elements needed for protein synthesis, replication, transcription, and assembly in their genomes [13]. Because the members of the variola-vaccinia subgroup do not appear to differ in their physical or chemical features, biological traits have been utilised to distinguish them [14]. The virus is resistant to ether and desiccation. Heat stability tests revealed that 20 minutes of heating at 40°C had little to no impact on infectivity but that 20 minutes of heating at 50°C or 56°C completely eradicated it [15]. The vaccinia vaccination offered coincidental immunity to the MPV before smallpox was eradicated and, consequently, there was no longer a need for vaccination [16]. It has a mysterious natural reservoir. However, some rodents and non human primates have been reported to contract the MPV naturally. The MPV incubation period lasts between 6 and 21 days. The period of communicability is from 1-2 days prior to the rash to when all scabs have fallen off or have disappeared [17].

Though it is a DNA virus, in infected cells' cytoplasm, it completes its life cycle. The genes that code for housekeeping tasks are widely conserved among various pox viruses, but the genes that code for

interactions between the virus and the host are less conserved and are found near the terminal region. Every protein needed for viral DNA replication, transcription, and virion assembly is encoded by the MPV genome [18]. The MPV's morphology reveals that virions are geometrically corrugated surfaces around ovoid or brick-shaped particles. MPV size ranges mostly between 200-250 nm [19].

Epidemiology

Monkey pox cases have been reported from 10 African countries between 1970 and 2019 [3]. Outside Africa, in 2003, 53 people from USA were affected with the West African clade following contact with infected pet dogs [20]. There were no deaths despite 26% of patients being hospitalised, including a 10-year-old with encephalitis. A few cases from different nations between 2018 and 2021 were reported without any fatalities, five of these cases were in Nigerian travellers who were returning home [21]. A case of monkeypox was reported from the UK in a traveller who had returned from Nigeria on 6th May 2022 [22]. Since then, an exponential increase was seen in people with no history of travel to endemic areas. Between 1st January 2022 and 22nd July 2022, 16,016 laboratory confirmed cases of monkeypox and five deaths have been reported to WHO from 75 countries/territories/areas in all six WHO regions [23]. On July 23rd, 2022, the WHO declared MPV as a Public Health Emergency of International Concern (PHEIC) [24]. As of July 24, 2022, India had four MPV instances; the first incidence had been recorded on July 14, 2022. The man, who travelled from the United Arab Emirates to the southern Indian state of Kerala, India. The final instance came from Delhi, although the other two were from Kerala and had histories of international travel [25]. Changes in the biologic makeup of the virus, climatic change, declining immunity following the end of smallpox vaccination, increasing international travel following the release of COVID-19 limitations, high-risk sexual behaviour populations have all been linked to the resurgence of monkeypox [26]. As per phylogenetic analysis showed, MPV causing the current outbreak is belongs to clade 3, which is closely related to the virus causing the sporadic case in Maryland, USA in 2021, which, in turn, was related to the clade 2 viruses of Nigerian outbreak in 2017-2018 [27]. Mainly adult homosexual males have been affected. There is possibility of transmission of infection from human to animals and this is the thing of concern which may then serve as a recurrent source of infection [28].

Pathophysiology

After entering the body, the MPV multiplies at the injection site before spreading to nearby lymph nodes. The virus spreads and seeds to more organs following vireamia. The period of incubation last upto 21 days. Beginning of symptom is linked to secondary viremia, which results in a prodromal stage of 1-2 days, including fever and lymphadenopathy, before lesions manifest. Those who are unwell right now run the risk of spreading the disease. Oropharyngeal lesions can rise to skin lesions. Serum antibodies are frequently detectable when lesions arise [29].

The cytoplasm of the infected cell serves as the site for the replication of the linear two-chained DNA genome of poxviruses. Both the Extracellular-Enveloped Virus (EEV) that cordially extrudes by connecting with actin tails, and the Intracellular Mature Virus (IMV), which only releases itself when infected cells die and lyse, are viruses that can infect humans. Poxvirus-infected cells produce their own virions. The primary mechanism for the rapid spread of the virus in the infected host is believed to be the release of EEV from infected cells [30]. The external membrane of the IEV merges with the plasma membrane and remains affixed to the cell surface after being carried to the cell periphery by microtubules, creating Cell-Associated Virions (CEVs). CEVs are in charge of managing cell connectivity. The MPV incubation period lasts between 6 and 21 days. The period of communicability is from 1-2 days prior to the rash to when all scabs have fallen off or have disappeared [31].

Routes of Transmission

The disease is transmitted from both animals to humans and man-to-man [11]. MPV is transmitted when an individual comes into contact with an animal, contaminated objects, or materials or through skin wounds, it enters in the body through respiratory system openings, or mucosa in the mouth, nose, eyes. A person can become infected by an animal bites, animal scratches, cooking bush meat, direct exposure of various body fluids or lesion, or indirect exposure, like contaminated linen. Large respiratory droplets are thought to be primarily responsible for man-to-man spread [1]. Monkeys, squirrels, Gambian pouched rats, dormice, and non human primates are examples of natural reservoirs that are widely known. The secondary attack rate among household contacts is less than 10%, unlike smallpox, where it was 35-88% [32]. The transmission of MPV through direct sexual contact is not certain but intimate skin and mucosal contact during sexual activity can contribute in the spread of infection of MPV. Congenital MPV in newborn has been reported suggestive of vertical transmission. Vertical transmission and foetal deaths have been described [33]. The sexual transmission of seminal or vaginal fluids is not definitively demonstrated.

Pathogenesis

The MPV multiplication takes place at most likely fixed or mobile connective tissue cells. At the site of infection MPV multiplies followed by cell necrosis, phagocytosis and vasculitis. These early cellular responses appear to be precursors to the transmission of viruses to other cellular loci through regional lymphatic and vascular channels. From the blood, MPV moves to the spleen, tonsils, and bone marrow before passing through the lymph and ending up in nearby lymph nodes. In these organs, there is a consistently detectable level of viremia with subsequent virus release. It is assumed, that at this stage, the virus is transferred to the target organs, where it results in a condition that may be seen clinically [34].

Clinical Features

There is similarity between the clinical features of smallpox and monkey pox. As lymphadenopathy is seen in 90% of unvaccinated patients but is uncommon in smallpox, it is one of the key factors in differentiating monkeypox from smallpox. Classically, the prodromal phase lasts 1-3 days before the maculopapular rash. The clinical progression is similar to that of typical smallpox lesions and the mean diameter of the lesions ranges between 0.5 and 1 cm. The key clinical characteristic that sets MPV apart from smallpox is the presence of lymphadenopathy [35]. Following the prodromal phase, the exanthema phase is characterised by vesiculopustular rashes that start on the face and extend across the body between 1-10 days. Lesions in MPV patients simulate lesions of smallpox and are monomorphic, pea-sized, and rigid. Smallpox cannot be confused with MPV lesion because of its crop-like appearance and weak centrifugal spread [36]. Undiagnosed acute rash with one or more symptoms, such as a headache, a sudden onset of fever, back discomfort, asthenia, myalgia, and lymphadenopathy indicates diagnosis more towards MPV [37]. Fever, headache, myalgia, and lymphadenopathy are among the early signs of monkeypox, which sets it apart from smallpox. Skin lesions on the face, extremities, especially the palms and soles, mucosal lesions in the mouth start to manifest after one to two days. These lesions are centrifugally concentrated, from a few to thousands of lesions may be present overall, and the rash may or may not spread to other parts of the body [38]. The subsequent two to four weeks, the lesions go through macular, papular, vesicular, and pustular phases at one to two day intervals. Lesions measures in size from 2-10 mm and change synchronously. Lesions stay in pustular phase for five to seven days before developing crusts. Usually illness subsides within three to four weeks after the symptoms starts, lesions heal with crust formation which sheds off during next one to two weeks. Once all crusts have fallen off, patients are no longer contagious [36]. OPV antigens

are visualised via electron microscopy, immunohistochemical staining, and serum tests for anti-OPV IgM and IgG [38]. Smallpox, generalised vaccinia, disseminated zoster, chickenpox, eczema herpeticum, disseminated herpes simplex, syphilis, yaws, scabies, rickettsia pox, measles, bacterial skin infections, drug-associated eruption are some of the differential features in monkey pox [39,40], but lymphadenopathy has been observed to be the characteristic feature of monkeypox.

Contact Tracing and Contact Monitoring [41]

Case definitions are explained as per WHO newsletter dated 19th May 2022 is given in [Table/Fig-1]. If a person has had one or more of the exposures listed below within the time frame beginning with the onset of the source case's initial symptoms and ending when all scabs have gone off, they are deemed to be a contact. Contact tracing followed contact monitoring is depicted in [Table/Fig-2].

Suspected case	Probable case	Confirmed case
A person of any age exhibiting an unexplained acute rash and one or more of the following symptoms must have a history of travelling to impacted countries during the previous 21 days. enlarged lymph nodes, fever, headache, muscle aches, and extreme weakness.	A individual who meets the criteria for a suspected case, has a clinically compatible illness, and is connected to the community epidemiologically (direct physical contact with skin or skin lesions, including sexual intercourse, or contact with contaminated things like clothing, bedding, or utensils is suggestive of a strong epidemiological relationship).	Situation in which the MPV has been detected in the laboratory (by Polymerase Chain Reaction (PCR) or sequencing identification of specific viral DNA sequences).

[Table/Fig-1]: WHO definition of suspected case, probable case and confirmed case [41].

Contact tracing	Contact monitoring
1. Face-to-face exposure. 2. Direct physical contact. 3. Contact with contaminated materials. 4. Identifying information Cases can be asked about contacts at home, at work, at school or in the nursery, about sexual contacts, about healthcare, about places of prayers, about transport, about sports, and about any other recalled encounters.	1.Monitoring of contact should be done daily for the onset of signs/symptoms for a period of 21 days from the last contact with a patient or their contaminated materials during the infectious period. In case of occurrence of fever clinical/lab evaluation is warranted. 2. Donation of blood, cells, tissue, organs or semen of asymptomatic contact should be prohibited while they are under surveillance. 3. Preschool kids should not be sent to day care, nursery. 4. Health professionals should be under active surveillance for symptoms for 21 days after unprotected exposures to patients with monkeypox or potentially contaminated materials if they are asymptomatic.

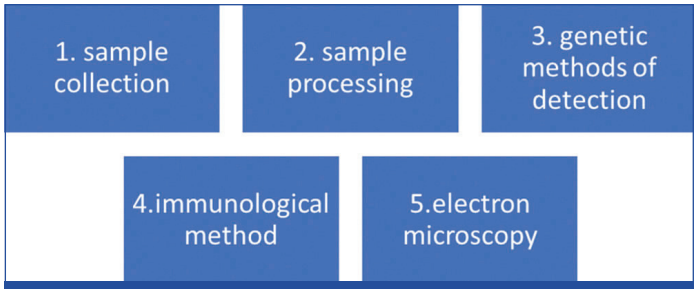
[Table/Fig-2]: WHO definition of contact tracing and contact monitoring [41].

Laboratory Diagnosis [42]

Laboratory diagnosis is done in following manner as shown in [Table/Fig-3] and elaborated as follows:

Genetic methods: The E9L-NVAR and B6R assays target OPV DNA polymerase and extracellular enveloped protein genes, respectively. RT-PCR or PCR is required for this test, and it is advised that it should be performed at a Biosafety Level 3 facility [43]. Restrictions Length Fragment Polymorphism (RFLP) of PCR-amplified genes or gene fragments is another method for detecting MPV DNA [44].

Immunological methods [45]: For the identification of IgG and IgM antibodies and viral antigens, this involves the use of immunohistochemistry and the enzyme-linked immunosorbent test. Using antibodies either monoclonal or polyclonal against all OPVs, immunochemistry analysis can be performed to differentiate poxvirus infection from herpes infection. It is known that both cellular response and humoral response increases at beginning of an illness. An indirect MPV diagnosis may be made if IgG along with IgM antibodies are discovered in an uninfected person who presented with typical rash and critical sickness. But none of these methods are exclusive to MPV [45].

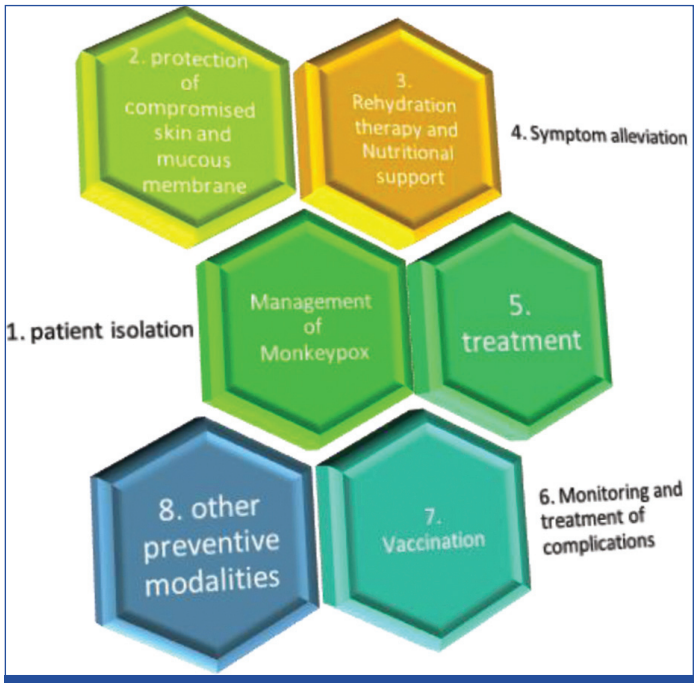


[Table/Fig-3]: Steps for laboratory diagnosis.

Electron microscopy: Under an electron microscope, MPV has an intracytoplasmic brick-like appearance. Other pox virus species cannot be distinguished morphologically, hence this method cannot provide a conclusive diagnosis, but it gives a clue that the virus belongs to the *Poxviridae* [46]. According the immunohistochemical and histopathology examinations done by Osorio JE et al., MPV antigen was found in the tissues of various organs like ovary, brain, heart, kidney, liver, pancreas etc., [47].

Principles of Management [42]

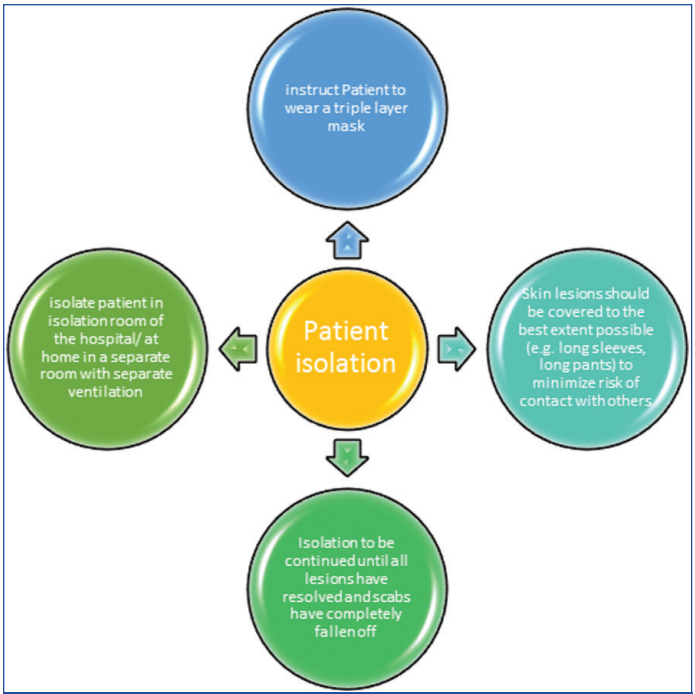
Management of monkeypox is simplified in diagrammatic representation as follows in [Table/Fig-4].



[Table/Fig-4]: Flowchart management principle of monkeypox disease.

Patient isolation: Patient isolation plays key role and is shown in [Table/Fig-5] [42]. Eye pain, blurred vision, shortness of breath, chest pain, difficulty in breathing, altered consciousness, seizure, production of urine is reduced, and decreased appetite should all be closely monitored in the patient. Instructing the patient to wear a triple layer mask during patient isolation. Long sleeves and long pants are the good options for covering skin lesions to reduce the chance of spreading of infection with others. Keep patient in separate room in hospital or home with separate ventilation till lesions are healed and scab gone off [42].

Treatment: Treatment of MPV is symptomatic and supportive [1]. Cidofovir has antiviral activity against a variety of viruses by inhibiting viral DNA polymerase. CMX-001 is a modified cidofovir compound has less nephrotoxicity as compared to that seen with cidofovir. Release of the virus from the cell is blocked by medicine ST-246, and has shown good activity against a various OPV species [48]. The prognosis relies on variables; including previous immunisation history, beginning health state, present disorders, co-morbidities. Tecovirimat is available as oral (200 mg capsule) and injection



[Table/Fig-5]: Patient isolation protocol [42].

for intravenous formulations. Brincidofovir (CMX-001) has lesser nephrotoxicity and it is modified cidofovir [49].

The vaccines for monkeypox are:

1. **ACAM2000:** Live vaccinia virus with single-dose administration [48].
2. **LC16m8:** Weakened vaccine virus a single dose of medication. It demonstrates a safer profile and fewer adverse effects in both human and animal vaccines than ACAM2000 [48].
3. **Modified vaccinia Ankara; IMVANEX (Europe) and IMVAMUNE (US):** Attenuated virus occasionally replicates in mammalian cell. It is depicted that modified vaccinia Ankara is safe and encourages the formation of antibodies in people with atopy and weaker immunity, which are contraindications for administering live vaccinia. No lesion appeared at the immunisation site [50].

Prevention

It is well known that people who had got the smallpox vaccine had superior MPV protection or experienced less severe sickness than people who had never received the vaccine. These vaccines are currently not recommended for mass administration but are recommended for postexposure prophylaxis preferably within four days to two week of exposure and for pre-exposure prophylaxis in high-risk individuals including healthcare workers [51]. To prevent an outbreak include, high index of suspicion, early identification, isolation, barrier nursing, and strict infection prevention practices by healthcare workers are essential [52].

CONCLUSION(S)

It was previously thought to be a rare zoonotic infection. After decades of dormancy, MPV has re-emerged as a clinically significant condition. Monkeypox has an overall case-fatality rate of upto more than 10%. Herd immunity is decreased as a result of cessation of smallpox vaccination due to eradication of the disease. As a result of climate change and deforestation and bush meat consumption, there is increased contact between human and potential MPV animal reservoir host. MPV is no longer confined to endemic regions as travellers have exported it. Mode of transmission is by human to human and with animal reservoir. A global emergency has been declared regarding MPV, and the incidence of disease may increase. Since MPV has not previously been linked to India, clinicians' knowledge of the infection is restricted, diagnostic tools are scarce, the course of the illness and its treatment are little characterised, and treatments and preventive measures are also poorly understood. Clinicians should follow the protocol for diagnosis, reporting, and isolation of cases, maintain a high index of suspicion for this illness, as well as dispel public fears and misconceptions. Even though the disease in non endemic nations has received attention globally, effort should be paid to controlling the disease in Africa, where the majority of deaths still occur. Future generations should remember to pay attention to neglected tropical illnesses.

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