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Global Attention to Monkeypox

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Monkeypox is brought on by a pox virus that is closely linked to the smallpox virus and is spread by intimate contact between humans and animals. When people come into contact with sick animals, they may unintentionally contract the monkeypox. Smallpox vaccinations cross-protect against MPXV due to antigenic similarities. Fever, headache, muscle aches, lymphadenopathy, and a recognisable rash that later develops into papules, vesicles, and pustules that scab over and recover are all signs of monkeypox (MPX). There are now two vaccines on the market: JYNNEOSTM (live, replication incompetent vaccinia virus) and ACAM2000® (live, replication competent vaccinia virus). Antivirals (such as tecovirimat, brincidofovir, and cidofovir) and vaccinia immune globulin intravenous (VIGIV) are available as therapies for monkeypox, albeit the majority of cases will have moderate and self-limited disease and supportive care is often sufficient. The

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ongoing outbreak, which has more than 10,000 cases in more than 50 nations between May and July 2022, illustrates how easily MPXV can spread among people and how this could pose a serious threat to public health with worldwide repercussions.

Keywords: Monkeypox; MPXV; zoonosis.

1. INTRODUCTION

The monkeypox virus, a member of the Chordopoxvirinae subfamily of the Poxviridae family and the Orthopoxvirus genus, is the culprit behind monkeypox, a currently uncommon zoonotic illness. [1] The virus has double-stranded DNA. The virus was first identified in monkeys in a Danish lab in 1958, which is where the name "monkeypox" comes from. [2] In 1970, a 9-month-old baby boy in Zaire (now the Democratic Republic of the Congo, DRC) was found to have the first instance in humans.[3] Monkeypox has since grown endemic in the DRC and has spread to other African nations, primarily in Central and West Africa. 2003 saw the first instances of monkeypox outside of Africa.[4] Monkeypox. When transmitted from person to person, the monkeypox virus takes 12 days to incubate.[5] The monkeypox virus shares morphological characteristics with other Orthopoxviruses.It is 200–250 nm in size, brick-shaped, enclosed, and composed of a core component and surface tubules.[6]

2. EPIDEMIOLOGY

In the DRC, the first case of human monkeypox was identified in 1970.[7] Following that, between 1970 and 1990, more than 400 cases of monkeypox in Africa were recorded. The bulk of these were diagnosed at DRC.[8]6 cases later, in the Central African Republic (CAR) two instances in Cameroon Nigeria: 3 instances Ivory Coast: two instances 1 case each in Gabon and Sierra Leone, 4 cases in Liberia, 58 cases.[9]47 cases of confirmed and suspected monkeypox, all which were contracted through contact with domestic prairie dogs, were documented (Cynomys spp).[10]The first outbreak of human monkeypox was reported from the Republic of Congo (ROC) in 2003. In this outbreak, there were 11 confirmed and probable cases of monkeypox, all of whom were under the age of 18, and one fatality. The virus that causes monkeypox has reportedly spread from person to person six times in a row, setting a record for the longest straight sequence of human-to-human monkeypox transmissions. Between September and December 2005, five villages in Unity State, Sudan, reported ten confirmed and nine potential cases of monkeypox (2 in Bentiu, 3 in Modin, 5 in Nuria, 5 in Rubkona, and 4 in Wang Kay).[11] Various numbers of monkeypox cases were reported between 2010 and 2018 in a number of African nations, including the DRC, CAR, Cameroon, Liberia, Sierra Leone, as well as COA. 82 Additionally, a 2017 report claimed that an outbreak was occurring in Nigeria. Between September 2017 and September 2018, 122 confirmed or potential cases of human monkeypox were reported in 17 states of Nigeria. There were six fatalities reported (case fatality rate: 6%).[12] Multiple cases of monkeypox were discovered in the UK on May 20, 2022.[13] After May 2022, numerous cases of monkeypox were confirmed in non-endemic nations all over the world. Monkeypox was classified as an "evolving threat of moderate public health concern" by the WHO on June 23 as a result of this atypical outbreak. Additionally, on July 23, 2023, the WHO declared the monkeypox outbreaks in numerous nations and areas to be a "Public Health Emergency of International Concern" (PHEIC).[14] As of 13 September 2022, 57,995 monkeypox virus infections which were laboratory confirmed have been reported in >100 countries or regions across all six WHO regions.[15] Nine different nations reported a total of 18 deaths from this group. In particular, relatively recent news reported that on September 6, monkeypox was confirmed in the first person in Hong Kong.[16] Four MPX cases had been recorded in India as of July 24, 2022; the first case had been reported on July 14. They were all men. The first three cases were from Kerala and had prior international travel, but the final instance was from Delhi and had no prior international travel.[17]

3. TWO STRAINS OF MONKEYPOX VIRUS: CENTRAL AFRICAN AND WEST AFRICAN

The genomes were analysed to see whether the monkeypox strains from Central and West Africa varied in pathogenicity. Chen et al. compared three West African strains with a Central African strain (ZAI-96), finding that there was a 0.55–0.56% nucleotide difference between the Central

African strain and the West African strains. Such genomic testing demonstrated that the two virus strains could be distinguished on a phylogenetic tree. The Central African strain is expected to contain 173 functional unique genes, while the West African strain is predicted to have 171 unique genes, according to further research of the Central and West African strains by Chen et al. At the protein level, they have 170 orthologous proteins in common and are 99.4% similar. The transcription regulatory sequences in the two genomes did not differ significantly from one another. The authors looked at the 56 virulence genes, 53 of which are shared by both strains, because there is a variation in virulence between the two strains. There are 276 substitutions, accounting for 61 conservative, 93 non-conservative, and 121 silent amino acid changes, among these 53 genes. The anticipated lengths of sixteen proteins have changed, mostly as a result of N- and C-terminal extensions. The orthologs of BR-203, BR-209, and COP-C3L are where the two strains diverge most noticeably from one another.[18]A similar group of genes were described by Likos et al. as potential candidates to explain the variation in virulence between the two strains.[19]

4. MECHANISM OF INFECTION

The vaccinia virus, a member of the Poxviridae family, has a protein called E3 that prevents the host cells' innate defences from activating after infection and keeps the replication process going. Likewise, the monkeypox virus has a protein that is identical to E3 and performs similar roles.[20] The monkeypox virus can infect people using two different virions. The first is made possible by internal mature viruses (IMV), whereas the second is made possible by exterior envelope virion (EEV).[21] Research have demonstrated that this EEV virion is what causes the virus to propagate so quickly within the host's body. Some microtubules aid in the movement of the intracellular enveloped virus into the host cell. Moreover, they help the virus adhere more firmly to the surface of the host cell. Another type of virion known as CEV, or the cell associated virion, enables the virus to propagate between cells.[22] One of the noteworthy details provided by Hutson et al. illustrates the potential for tissue tropism. Increased viral load and infection through many virions were confirmed by the isolates from the dead animals that were the disease's victims. The precise mechanism of action is difficult to comprehend due to the animal source's unpredictability. Owing to this variation, the virus's contact with the host may alter, which could affect how the immune system is activated.[23]

sequential events of rash evolve during monkeypox virus infection:

Macules: lesions with a flat base
↓
Papules: slightly rise firm
↓
vesicles: lesions filled with clear fluid
↓
pustules: lesions filled with opaque fluid, sharply raised
↓
Scabs: dry up and fall off

5. CLINICAL FEATURES

The incubation period lasts anywhere from 5 to 21 days, but most commonly 6 to 13 days.[24] All ages are impacted, but the median age has increased over time[25]Men are affected more than women. Smallpox and other illnesses caused by the pox virus have clinical characteristics.[26] The prodrome and the rash are the two distinct stages of monkeypox in humans. Infection with the monkeypox virus causes the following initial symptoms: rashes, headache, fatigue, fever, backache, lymph nodes swelling, chills or sweats, sore throat, muscle aches, and lymphadenopathy. The rash typically emerges a few days after lymphadenopathy and a fever. Rash is characterised by a few to several thousand lesions and typically begins on the face before spreading to the entire body. Plaque is gradually replaced by papules, blisters, pustules, and scabs over the course of 2-4 weeks as the rash worsens, followed by shedding. Monkeypox symptoms span 2-4 weeks, and the condition is typically self-limiting. Patients infected with the CA clade of the virus often have greater mortality rates than those infected with the WA clade of the virus following infection. The lethality of monkeypox patients depends on the clade of virus infected, route of infection, and patient age.[27]

6. TRANSMISSION OF MONKEYPOX

Human-human and animal-human transmission are the two potential MPXV transmission routes. Inter-human transmission has been linked to respiratory droplets, contact with bodily fluids, contaminated patient objects or surroundings, and skin lesions on sick individuals. According to reports, the Congo Basin clade (Central Africa clade) is more virulent than the West Africa clade

and so makes a greater contribution to inter-human transmission.[28] Direct contact with any of the aforementioned naturally occurring viral hosts or ingestion of these hosts is how animal-to-human transmission, sometimes referred to as zoonotic transmission, takes place. Furthermore, zoonotic transmission may take place through direct contact with blood, bodily fluids, and inoculation from mucocutaneous lesions of an infected animal.[29] As of right now, no reports of human-to-animal transmission exist. The CB clade has significantly greater rates of serial transmission events, secondary attack rates (SARS), and human-to-human transmission than the WA clade [30] For the CB clade, the Ro, or contagious disease rate, ranges from 0.6 to 1. Although the Ro for the WA clade is unknown, it is predicted to be substantially lower than CB. The greatest limit in the CB example indicates that the infection is likely to spread throughout the human population rather than being contained to a single individual.[31]

7. STRUCTURE OF VIRUS

When observed under an electron microscope, the monkeypox virus has a brick-like structure. A lipoprotein layer surrounds the outer region.[32]A linear core with a double-stranded (ds) DNA genome and the viral replication and uncoating enzymes surrounds the encapsulated virion portion.[33] The outer lipoprotein-rich layer also protects the virus's centre area, which contains many transcriptional components as well as all of the interconnecting connections and the dsDNA genome. With two lateral zones on either side of the disc, the middle portion resembles a biconcave disc.[34]The genome of the monkeypox virus is over 197 kb in size.[35]structural proteins and other crucial enzymes produced by the monkeypox virus share 96.3% of their genome sequence with the smallpox virus, however there are major differences between the two viruses' encoding for host-range factors and host cell pathogenicity (closer to the terminal genomic part)[36]Several proteins contribute to the monkeypox virus's increased virulence, whereas others have the opposite effects. The monkeypox virus contains one of the most dangerous genes, homologous to BR-203, which prevents infected lymphocytes from going through apoptosis.[37] MOPICE (monkeypox inhibitor of complement enzymes) and BR-209 are two examples of other homologous genes. By preventing IL-1 from interacting with the inflammatory cytokine IL-1, the BR-209 interferes with the host's defence mechanism and prevents virus entry into the host cells.[38].

8. PATHOLOGY

According to pathological findings, the monkeypox virus can be found in the lungs, ovary, heart, kidney, brain, and other organs. The ovarian tissues had the highest viral load out of all of these organs, indicating that these tissues are more likely to contract the monkeypox virus.[39] Transdermal, nasopharyngeal, and oropharyngeal ingestion are the three possible entry points for the virus into the host cells. The monkeypox virus can, according to observation, travel through blood to reach internal organs. The monkeypox virus begins to replicate itself in the lymphatic systems that supply the blood during the incubation phase. Then, it spreads to other body organs via the blood.[40] Before being noticeable on the skin, rashes first develop in the oropharyngeal areas.[41] The rate of the rashes' spread is unpredictable, and it could be considerably slower or, in some circumstances, very concentrated.[42] The lesion count can be used to categorise the severity of a disease because larger lesion counts are associated with a higher likelihood of serious consequences.[43] Individuals who have severe complications may develop encephalitis, septicaemia, ocular infections that result in irreversible visual loss, respiratory and gastrointestinal problems, and encephalitis-related symptoms. MPXV can be vertically passed from the mother to the foetus during pregnancy. Only one of four MPXV-infected pregnant women in research conducted in the DRC gave birth to a healthy child. One woman gave birth to a stillborn child, while two women miscarried during the first trimester. Skin lesions were seen all over the body of the stillborn.[44] In a different investigation, lesions were seen on the maternal surface of the placenta in four out of five MPXV-infected women in the DRC who experienced foetal death. The investigations did not specify which clade of MPXV these individuals had been exposed to, but given the research geographic context, it is highly likely the Central African clade.[45] According to a study done in Zaire between 1980 and 1985, MPXV infection in young children is more likely to be deadly than in adults. The case fatality rate in MPXV-infected children between the ages of 0 and 4 years was 14.9%, compared to 0% in adults aged 10 or older. Their immunological responses may differ in several ways, which could explain this disparity.

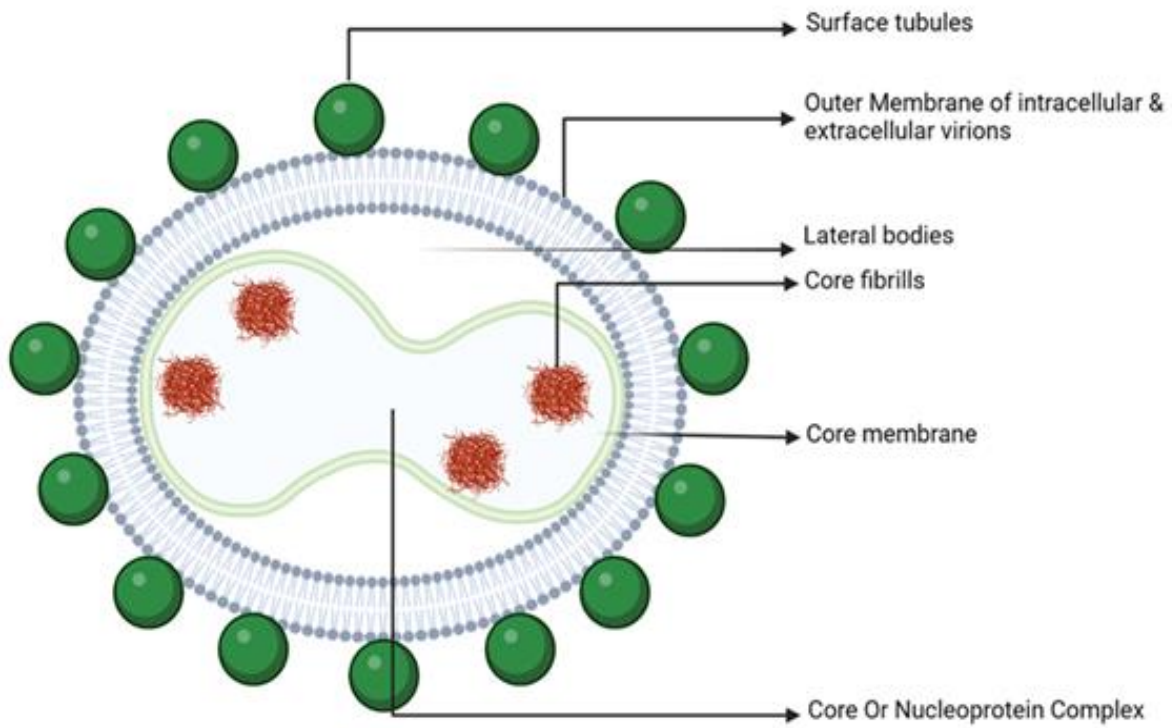

Fig. 1. Structure of a Virus

9. DIAGNOSIS

The numerous diagnostic laboratory techniques include tissue immunohistochemistry, viral isolation, serology, electron microscopy, and molecular diagnostics. The Recombinase polymerase chain reaction (RT-PCR) and other molecular testing restriction-fragment-length amplification (RPA), loop-mediated isothermal amplification (LAMP), and (RFLP), polymorphism, etc. Test using real-time PCR (RT-PCR) on samples taken from blood, throat, skin lesions, and Urine has a strong sensitivity and specificity for MPX diagnosis. However, the cost of these testing is high, not accessible commercially. Guidelines have been given by the Indian government for MPX diagnosis in patients. samples, such as skin scrapings, serum urine, EDTA blood, and nasopharyngeal samples Orthopox genus-specific PCR will be performed on the oropharyngeal swab. The samples will be prepared for MPX-specific PCR if the results are positive.[46] Enzyme-linked immunosorbent assays (ELISA), western blots (WB), immunohistochemistry, and others are also used in laboratories to identify monkeypox. Electron microscopic observation can be used as an auxiliary method to detect monkeypox virus [47]

10. VACCINATION

Studies have demonstrated that smallpox immunisation offers cross-protection against other OPV species, such as MPXV. Approximately 90% of the cases that have been documented are naive to OPV infection, and many of them were born after the smallpox eradication operation was discontinued.[48] It was found that people who had previously had the smallpox vaccine had 85% protection against MPXV [49] There are now two smallpox vaccinations on the market: ACAM200 and JYNNEOSTM. However, even after smallpox was eradicated, several nations continue to keep vaccination stockpiles.[50] It is possible to employ the doses of the Ankara vaccine, a live vaccination that confers immunity against both smallpox and monkeypox. When compared to the outdated vaccinia vaccine, receiving two doses of the vaccine within four weeks will produce positive benefits.[51]The Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have also granted licences to IMVAMUNE, a replication-deficient, attenuated third generation modified vaccinia Ankara (MVA) vaccine, for the prevention of smallpox and monkeypox in adults (18 years of age or older)

who have been found to have a high risk of infection with VARV and MPXV.[52]

11. TREATMENT

Most patients recover without treatment since the symptoms of the monkeypox sickness are typically minor. According to CDC recommendations, infections with the monkeypox virus do not yet have a specific therapy. Monkeypox disease can be treated with antiviral medications that have been licenced for the treatment of smallpox.

12. CIDOFOVIR

In vitro and preclinical investigations have shown that the antiviral drug cidofovir (Vistide) is effective against poxviruses by inhibiting viral DNA polymerase.[53]Mice were given cidofovir therapy for two days after being exposed to the virus for 24 hours, which reduced viral loads and tissue and plasma levels of the cytokines interleukin (IL)-10, IL-6, IL-3, and IL-2.[54]When CDV treatment is started 24 hours after lethal intratracheal monkeypox virus infection, research has shown a significant decrease in mortality and cutaneous monkeypox lesions.[55]

13. TECOVIRIMAT

Small-molecule virus inhibitor Tecovirimat (also known as TPOXX, ST-246) is effective against Orthopoxviruses, including vaccinia virus, camel pox virus, cowpox virus, mousepox virus, variola viruses, and monkeypox virus, both in vitro and in vivo.[56]Inhibiting the transmission of viruses inside the body by preventing them from leaving infected cells, Tecovirimat targets the VP37 protein.[57]Neither the production of mature viruses nor the synthesis of DNA or proteins is inhibited by tecovirimat. Until cell lysis, the mature virus stays inside the host cell. With an EC50 range of 0.01 to 0.07 μM, the antiviral effectiveness of tecovirimat was quite significant.[58] Numerous studies have shown that the VP37 protein is crucial for forming enveloped viruses by encasing intracellular mature viruses in membranes generated from the Golgi.[59] In the monkeypox model, treatment with tecovirimat 10 mg/kg for 14 days could result in >90% survival.[60] By administering tecovirimat once daily orally, it was discovered to be effective in protecting nonhuman primates (NHP) from monkeypox virus infection. The treatment group showed significantly lower viral loads, fewer rashes, prolonged survival, and lower mortality rates than the control monkeys.[61]Following studies demonstrating its safety for use in humans and efficacy in treating animals infected with related viruses, the FDA approved its initial use for treating smallpox in 2018.[62]The tecovirimat (600 mg twice day for 2 weeks orally) was shown in a trial on monkeypox patients to have no side effects and to shorten the duration of the illness and virus shedding.[63]In addition, data gathered from 25 cases who had finished a course of tecovirimat therapy and had been diagnosed with monkeypox infection showed that all of the cases had handled the antiviral medication well, with just minor side effects. By day 7 of treatment, the lesions and pain had totally disappeared for 10 patients (or 40%), and for 23 out of 25 patients by day 21. The most common side effects of medication were diarrhoea in 2 patients (8%), itching in 2 patients (8%), nausea in 4 patients (16%), headache in 5 patients (20%), and exhaustion in 7 patients (28%).[64] Tecovirimat treatment for monkeypox patients is now available thanks to an expanded access investigational new drug (EA-IND) protocol created by the CDC and FDA. The Cedgruiontres for Disease Control also collected data on 1001 cases that received this antiviral medication in total [65] According to the most recent data, numerous clinical investigations (PALM-007, PLATINUM, WHO/ARNS, and ACTG5418) are now being conducted or are scheduled to do so in order to determine the safety and efficacy of tecovirimat in treating individuals with monkeypox.[66]

14. BRINCIDOFOVIR

The FDA granted Brincidofovir a licence in 2021 to treat both adult and paediatric cases of human smallpox illness. The CDC is currently creating an Expanded Access Investigational New Drug to enable the use of brincidofovir for treating monkeypox.[67] In compared to cidofovir, brincidofovir has better oral bioavailability, improved antiadenoviral activity, and no nephrotoxicity. It also has higher intracellular levels of the active drug.[68] During an outbreak, monkeypox can be treated with VIGIV (vaccinia immune globulin intravenous).

15. PREVENTION

To avoid contracting MPV, some precautions can be performed. This comprises,(1) Avoiding close contact with animals that may be carrying the MPV, especially in areas where the disease

known as monkeypox is common.(2) Isolate and put to death any animals thought to be viral reservoirs.(3) Keep your distance from anything that has come into contact with a sick person or animal.(4)The proper personal protective equipment (PPE), such as an N-95 mask, water-resistant gowns that cover the entire body, and double-layered gloves, should be worn by front-line staff caring for MPV-infected patients and other high-risk individuals who are anticipated to come into contact with the infected people. The smallpox vaccine is anticipated to offer some protection against MPV infection because of its shared genetic makeup. Due to the lengthy incubation period of the virus, the US CDC states that protection of MPV is expected if the vaccination is taken within four days of exposure to MPV. It is argued that such immunisation should offer full immunity to the condition.[69]

16. CONCLUSION

The disease burden from MPX will rise, and it has been deemed a global emergency. Since MPX has not previously been linked to India, clinicians' knowledge of the virus is limited, diagnostic tools are scarce, the course of the illness and its treatment are little characterised, and therapies 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 nonendemic 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. No one is safe in the current era of globalisation unless everyone is safe.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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