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Global monkeypox disease outbreak: Prevalence and treatment

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Abstract

Monkeypox is a zoonotic disease and caused by the monkeypox virus (MPXV). It belongs to the species of the orthopoxvirus family. Data from several sources, including epidemiological studies, case reports, and clinical trials were included in a thorough literature analyses. Monkeypox was more common in Central and West Africa. Additionally, the virus has been identified in other regions of the world including North America, Europe, and Asia. A feverish sickness and distinctive skin lesions, resembling smallpox, are the primary symptoms of the disease. Preventing serious consequences and secondary transmission requires early diagnosis and effective care. The main therapeutic strategies used include vaccination, antiviral medication, and supportive care. Despite not being created expressly for monkeypox, the smallpox vaccination has shown some promising results in reducing the serious illness. Additionally, antiviral medications such as tecovirimat and cidofovir lower down the morbidity and mortality. To create targeted treatments and improve treatment plans, further research is necessary. In order to lessen the impact of monkeypox on the world, improved monitoring systems, public health education, and international cooperation are reequired. The current study highlights the necessity for ongoing work in disease monitoring, prevention, and therapeutic improvements by providing a thorough assessment of monkeypox viral prevalence and available treatments.

Introduction

The monkeypox virus (MPXV) causes the zoonotic illness monkeypox. MPXV belongs to a *Poxviridae* family composed of a double-stranded DNA, subfamily *Chordopoxvirinae*, and genus *Orthopoxviruses* [1, 2]. Following reports of a pox-like sickness in monkeys, the disease was first identified as monkeypox in 1958 [3]. The first case of human monkeypox documented in the Democratic Republic of the Congo in 1970. Following then, the illness was discovered in various western and central African nations [4]. Human monkeypox cases have been identified more recently, starting on May 7, 2022, in the Middle East, the United States, the United Kingdom, and other nations. By May 23, 2022, Pakistan has seen two sporadic occurrences of the zoonotic monkeypox illness, which had already spread to 12 other nations. Two instances of monkeypox were found at Lahore Jinnah hospital, Pakistan, according to the medical staff of Lahore Services Hospital (LSH). The patients were segregated and given the appropriate care. Following the discovery of these instances, the National Institutes of Health (NIH) urgently advised the nation's healthcare facilities to treat illness with caution. MPXV main structural element has the form of a dumbbell and contains characteristic surface tubules. The brick-shaped monkeypox virus has an average diameter of 200–250 nm [5]. The virus is enclosed in a lipoprotein envelope with a linear double-stranded DNA genome [6]. The Central African group has a more severe disease effect and is more easily transmissible. The Central African genotype is far more deadly, with a high mortality rate of around 11% in the uninfected population, in contrast to the West African clade's favorable prognosis of less than 1% fatality rate. Gabon, the Central African Republic (CAR), Congo, Sudan, Nigeria, Liberia, the West Coast, Sierra Leone, as well as the USA (brought into the country from Ghana) all had outbreaks [7]. The monkeys were kept in Denmark at research center in 1959 it was the place where first time the pox like symptoms appeared in monkeys. The first evidence of this disease obtained when a newborn from Congo was admitted in Basankusu Hospitals On September 1, 1970 [8]. A virus like MPXV was found in the boy's condition that resembled smallpox. Six instances of a virus resembling the pox were reported during October 1970 and May 1971 from Nigeria and Liberia [9]. Numerous confirmed cases of this disease have been documented in Africa, Singapore, Israel, USA, and UK [10, 11].

Morphology, genome organization, and morphogenesis

MPXV morphology suggested that the viruses are spherical and enveloped by geometric lipoproteins containing curved outer membrane. The 200 to 250 nm size for MPXV is well recognized [9, 12]. The membrane and the tightly packed core are both covered by the outer membrane, which contains genome in the form of a double standard DNA about 200 kb size. Due to a fixation process artefact during electron microscopy, the core is described as biconcave and has lateral bodies on each side. MPXV typically varies in size from 200 to 250 nm and DNA molecule that is palindromic hairpin-joined at both ends [13]. Tandem repetitions, hairpin loops, and Open Reading Frames (ORF) make up inverted terminal repeats (ITRs).. Although, MPXV is a DNA virus and has the ability to complete its entire life cycle within the cytoplasm of the host cell. It is the genome of MPXV which encode every protein responsible for transcription process, DNA replication and assembly of virus particle [14]. The genes that produce housekeeping activities have undergone substantial conservation across OPVs.

Two contagious viruses such as subcellular mature viruses (IMV) and extracellular-enveloped viruses (EEV) are produced from poxvirus-infected cells (and probably MPXV as well). IMV exits when a cell is broken, however EEV leaves cells when it comes into touch with an actin tail. Even though VACV has the aforementioned qualities [15]. The membrane which is outer to the intracellular enveloped viruses (IEV) merge with the cell membrane and stays connected to the surface of cell, while the cell-associated virions (CEVs) only generated the intracellular enveloped viruses (IEV) is carried by microtubules to the cell periphery. Cell-to-cell dissemination is mostly caused by CEVs [16]. IMV is encased in a double membrane formed by the trans-Golgi system (TGN) [17]. This process results in the formation of IEV. IMV budding through the plasma membrane is another method for the generation of EEV, [18]. Although, this has not yet been observed for MPXV, however the prototype VACV may have a problem with virion morphogenesis, as a consequence, non-infectious packed particles (DPs) are formed [18, 19]. Additionally, MPXV fails to generate ATIs and

sequester IMVs in ATIs owing to a mutation in the *ATIP* [20, 21].

Transmission

Human-human and animal-human, the two probable MPXV transmission pathways include human contact. Respiratory droplets, contact with body fluids, contaminated patient items or surroundings, and skin sores on ill people have all been associated to human-to-human transmission. [22-24]. According to reports, compared to the West Africa lineage, the clade from the Central African Congo Basin is more lethal, so makes a greater contribution to inter-human transmission. Interaction with any of the natural things that had got infection and consuming of these organisms are the two main routes of animal-to-human transfer, often known as zoonotic disease transmission. Additionally, it may take place through direct interaction with the diseased, infected and injection from infections of the skin lesions of an infectious agent. For the CB and WA clades for MPXV, nosocomial transfer has been documented [25, 26], some cases showed that the infection transmit through sexual intercourse of infected individual [27]. There have been no reports of human-to-animal transfer. Serial transmission events, secondary attack rates (SARS), and human-to-human transmission are substantially higher in the CB clade than in the WA clade [28] [29, 30]

Diagnosis of monkeypox virus

Molecular Techniques

It is advisable to perform the test in a Biosafety Level-three facility because it employs real-time PCR (RT-PCR), or polymerase chain reaction (PCR) [31]. By using RT-PCR and the conserved portions of the DNA polymerase, genes of envelope protein (B6R), and the E9L, MPXV DNA may be routinely detected in clinical, veterinary, and MPXV-infected cell culture materials. *F3L* and DNA-dependent RNA polymerase are subunits of 18 and rpo18 [32, 33]. In order to identify MPXV DNA, restriction length fragment polymorphisms (RFLP) of PCR utilize the sequence that encodes reverse transcriptase. However, RFLP requires viral culture and is laborious. RFLP of PCR products may not be the suitable course of action in a clinical environment when assay speed and sensitivity are crucial. Gel electrophoresis and enzyme digestion are also necessary for RFLP of PCR products. The gold standard for characterizing OPVs is still whole-genome sequencing employing next-generation sequencing (NGS) techniques. The technique is pricey, and analyzing the data gathered calls for a significant amount of computational power. Therefore, NGS may not be the suitable technique for characterization, particularly in sub-Saharan African nations with limited resources. Despite the fact that RT-PCR is still the preferred approach for identifying MPXV on a frequent basis, it must be supplemented by field genetic sequencing techniques, such as Oxford Nanopore MinION provides real-time viral genome data, which is required for scientific evidence epidemiological treatments. In West African settings with limited resources, for the effective genomic monitoring of the Ebola epidemic, MinION field sequencing was deployed [34] .

Phenotypic approaches

The incubation time for MPXV, according to clinical diagnosis, is between four and twenty-one days. It is frequently accompanied by a rapidly growing disease with a wide range of symptoms such as lymph node hypertrophy, fever, muscle aches, muscle aches, strong asthenia, dizziness, pharyngitis, drench sweats, and lethargy. Between 1 to 10 days, vesiculopustular rashes appear on the face and spread throughout the body later define the exanthema phase of the prodromal phase. The person that is infected with monkeypox virus experiences hard and pea-sized sores that mimic smallpox. Due to crop-like morphology and modest centrifugal distribution, smallpox cannot be misidentified with MPXV lesion. Clinically, MPXV infection may be distinguished from smallpox by the presence of lymphadenopathy. Clinical case definition for MPX has been proven in a sample of 645 persons to have high sensitivity (93-98%) and poor specificity (9% to 26%) in the absence of laboratory confirmation [28]. However, MPX clinical case definition is critical for identifying instances reported during surveillance.

Immunological methods

IgG, IgM, and viral antigens are recognized by immunohistochemistry analyses and the enzyme-linked immunosorbent assay (ELISA). To distinguish between herpes virus infections and poxvirus infections, immunochemistry investigation was used by utilizing polyclonal or monoclonal antibodies. It has been shown that the onset of disease is correlated with an increase in antiviral antibodies and T-cell

responses. Furthermore, five to eight days after the commencement of the rash, serum IgM and IgG antibodies are often seen. If IgM and IgG antibodies are found in a healthy person with a history of severe sickness or a rash, an indirect MPXV confirmation may be made. All of the techniques, not only MPX-specific, are capable of detecting the different OPV species. IgM may be used by someone who has had smallpox vaccinations to identify whether they have MPX infection [35]. Recent exposure to OPV has shown by strong IgM capture by ELISA technique. Whereas a high IgG capture ELISA indicates past OPV therapy through vaccination or spontaneous infection [36, 37]. The existence of both IgG and IgM in a single flow showed strong indication that a person has previously OPV vaccination or exposure to a natural illness has recently been exposed to OPV. IgM is thus a marker of recent exposure to MPXV in patients who have had a smallpox vaccine in places where MPX is common.

Electron microscopy

Under an electron microscope, MPXV appears as an intracytoplasmic brick with peripheral items and a central core ranging from in size from 200 to 300 nm. While, OPV species are unable to be recognized morphologically, this approach cannot offer a reliable diagnosis. It might be a significant indicator that the virus belongs to the *Poxviridae* family.

Immunohistochemistry

According to studies, mice with a severe combination MPXV antigen were discovered to have it in their ovary, brain, heart, kidney, liver, hepatocellular, and lung tissues. Moreover, the ovulatory tissues had viral titers that were much higher than those of other tissues, showing that ovarian tissues were particularly vulnerable to MPXV [38, 39]. The salivary epithelial cells, follicular, and sebaceous tissues of the lip region were among the other tissues where the viral epitope was found [40]. As this virus has ability to infect wide range of species of animals and now humans so it become difficult to detect it from specific tissues of host [41]. For MPXV, lymphoid tissues are excellent hosts (**Table 1**).

Host immune responses to MPXV

PXVs have created a variety of mechanisms or tactics to subvert or exacerbate the immunity of the host to infection [43]. More research has been done on the pathophysiology and pathogenesis of MPXV, however the adaptive and innate immune responses to MPXV infection are still poorly known due to a lack of data. Naturally killer (NK) cells, which produce cytokines to directly destroy microbial cells, are a critical component of innate immunity and control the activity of other types of cells. Activating and inhibitory NK cell receptors engage with their ligands, such as MHC-1 molecules, to trigger NK cell stimulation or restriction. Granules are secreted by NK cells to carry out their killing activity (which contain perforin and granzymes) as well as cell-cell interactions. IFN- and TNF-, which NK cells produced during the early stages of infection, mediate inflammatory reactions in inflamed tissues and collaborate with dendritic cells to polarize Th1 cells [44, 45].

CAST was shown to be especially susceptible to MPXV and it has been shown that CAST mice are more vulnerable to infection after intranasal exposure due to lack interferon- response inside the lung. Similar to this, the low levels of NK cells in CAST mice contribute to their sensitivity to MPXV. Purified and grown in vitro using IL-15, CAST mice NK cells provided protection against MPXV [46]. MPXV infection causes alterations in natural killer cells and other lymphocytes number. They also claim that MPXV infection causes lymphadenopathy and lymphoid depletion in NHPs who have been exposed to MPXV [47]. The frequency of all natural killer cells (NK) subtypes, CD16, CD16+, CD56, CD56+ all considerably increased at day (7) after inoculation. The lymphatic system's NK cell population and makeup changed by 4.6% following MPXV infection, and the results about the co-receptor concentration (CXCR3, CCR5, CCR6, and CCR7) in each subgroup of natural killer cells suggested that the expression of the receptors was either slowed after the MPXV challenge [44]. Apart from CPXV, the involvement with cellular homeostasis of MHC class I coincides with the strategies utilized by CPXV to escape antiviral CD8+ lymphocyte T-cell responses, despite the mechanisms by which viruses evade the effects of anti-viral chemokines, inflammatory cytokines, and antigen presentation aren't well acknowledged [48, 49].

Prevention and treatment

The incidence of MPX increased 20 times, according to research published in 2010 that contrasted continuous monitoring data from the DRC's health

Table1: The most common available tests for detection of monkeypox virus [42].

Examination	Summary
Isolation and culturing of viruses	A patient's live virus is cultured and isolated.
Electron microscopy (EM) examination	Visualization of a clear picture of a viral particle
Immunohistochemistry	Check OPXV antigens
PCR	Help in identification of MPXV DNA markers
Anti-OPXV IgG	Anti-OPXV antibodies detected
Anti-OPXV IgM	Detect Anti-OPXV antibodies
Tetracore OrthopoxBio Threat	Presence of OPXV antigens

sector during the 1980s with data collected from the same medical supply in 2006-2007 [50]. In the 2003, pandemic in the United States, the CDC recommended smallpox immunization (ACAM2000TM) for symptom management while not disease prevention up to two weeks after MPXV infection [51, 52]. The concerns regarding the vaccine expense, the safety of using live vaccinia viruses, and the vaccine's uncertain effects on immunocompromised persons, the smallpox vaccine is presently neither accessible to the general population [52] nor utilized in MPXV endemic regions [53, 54].

Only sub-Saharan Africa is home to MPXV endemic nations, and this area of the globe is also where 71% of the world's HIV infections occur. Serious vaccine complications, such as gradual vaccinia (following the smallpox immunization, an uncommon but possibly deadly adverse response caused gradual skin and tissue damage), as well as potentially fatal side effects like bacterial meningitis and staphylococci pneumonia [55], are more likely to occur in immunocompromised people. Dryvax® [56] was one of the well-known vaccinations used in the worldwide smallpox eradication effort. However, it resulted in alarmingly high rates of cardiac problems in recipients, and serious responses were seen when it was applied to immunocompromised individuals [57, 58]. These worries led to the creation of a new reproducing smallpox vaccine near the conclusion of the smallpox elimination effort. The CDC does not suggest using either the second-generation immunization ACAM2000TM or the third generation modifying vaccinia ankara (MVA) vaccine Imvamune. ACAM2000TM is now recommended for use in MPX patients after exposure (up to 14 days) to alleviate signs but not surely avoid disease [51].

In term of immunogenicity, ACAM2000TM is comparable to Dryvax®, though regrettably it also often results in cardiac adverse outcomes [56]. The CDC has not yet issued any recommendations about the smallpox vaccination in immunocompromised individuals who have been infected to MPXV. However, as of 2015, the CDC has recommended using the Imvamune vaccine (when antivirals are not yet available) for people who have had smallpox exposure, and CD4 cell levels between 50 and 199 cells/mm^3. Those who have CD4 cell counts below 50 cells/mm^3 are not likely to benefit from the smallpox immunization. Presently this vaccine is considered efficient as ACAM2000TM completely suppressed the replication of virus whereas Imvamune does not show significant effect [57]. Smallpox vaccination is not advised by the Advisory Panel on Immunization Practices (ACIP) in any way before to an event for anybody outside of a select group, including field researchers, pediatricians, military personnel, health-care workers, and first-line responders who may be exposed to the OPXV virus [57]. Due to the shortcomings of the smallpox vaccinations now on the market, research into alternative treatments including immunoglobulin and antiviral medicines is crucial to averting severe or deadly OPXV infection in immunocompromised individuals.

Two well-known antiviral medications, ST-246 known as (Tecovirimat) and CMX001 known as Brincidofovir developed from the approved medicine cidofovir, were under development from November 2016 [59]. Despite being stocked in the USA, these two popular antiviral drug which originated from the well-known antiviral medicine cidofovir, FDA still considers the use of these two antivirals as prophylaxis to be an investigation new drug (IND) [51]. Animal trials regarding the utilization of these antiviral medications to successfully cure pox like illness have been effective, with no significant side consequences. The antiviral tecovirimat was found successful therapy for treating the monkeypox illness at initial stage and it also prevents sickness, according to phase I clinical research. The CDC suggested ST-246 during the USA epidemic [51]. The CDC was working on developing guidelines on the use of antiviral drugs for OPXV. According to the Centers for Disease Control and Prevention CDC, treatment called immune globulin has not been proven to be effective in treating the long-term effects of a disease

called smallpox. Therefore, the CDC suggests using a different treatment called vaccinia immunoglobulin (VIG) as a preventive measure for people with a weak immune system who have been infected with a related virus called MPXV [51].

Conclusion

Worries regarding its possible effects on public health are raised by the growing geographical range. Although the MPXV has no particular antiviral treatment, supportive care, immunization is essential for controlling the illness and halting its spread. The development of efficient antiviral medications and tailored vaccinations is a current area of study that shows promise for the creation of future preventative and treatment plans. To lessen the impact of the MPXV on the world, continued international cooperation, enhanced surveillance, and more public awareness are required. To combat monkeypox and prevent it from spreading to other people, it is necessary to educate the general population, patients, and medical professionals.

Conflict of interest

The authors declare no conflict of interest.

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