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Emergence of an old foe with new challenges: Monkeypox

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Abstract

Monkeypox virus, a zoonosis exists sporadically in the tropical rain forest of central and western Africa. Human monkeypox cases were not observed until the early 1970s, despite the monkeypox virus being discovered in 1958. After smallpox eradication, it has been considered the most extensive orthopox virus in humans with serious epidemic prospects due to the rising of human outbreaks in recent years. As of July 2022, monkeypox was announced as a public health crisis. Without understanding its emergence, epidemiology, and ecology, monkeypox has always been perceived as a rare and self-limiting disease. It is imperative that patient groups with high-risk factors and risks of nosocomial transmission should be given increased attention when responding to outbreaks. There is an increased risk of monkeypox being transmitted due to globalization, conflict, and environmental factors, so it is vital that surveillance capabilities are built in order to impart profitable information to design appropriate avoidance, preparedness, and response measures. A growing need exists for the training of health workers as well as the advancement and accessibility of appropriate diagnostic tests, immunization, and antiviral treatment options.

Keywords: Monkeypox, orthopoxvirus, lesions, re-emerged, vaccination

Introduction

The re-emerging zoonotic disease, monkeypox emerged by the monkeypox (MPX) virus exists as a member of the Orthopoxvirus genus, Chordopoxvirinae subfamily and Poxviridae family. In addition to monkeypox, there are camelpox, cowpox, vaccinia, and variola viruses in the Orthopoxvirus genus. Since the smallpox eradication in 1980, the monkeypox virus is the most extensive Orthopoxvirus affecting human populations. A monkeypox virus measures 200-250 nanometers in size when observed in an electron microscope which is relatively large. The lipoprotein envelope surrounds the linear double-stranded DNA genome of a Poxvirus, giving the virus its brick-like shape. (Alakunle, 2020; Kugelman, 2014)^[3, 13]. Poxviruses make use of ribosomes for mRNA translation, but the genome also contains all replication, transcription, assembly, and egress proteins (Walsh, 2017; Alakunle, 2020)^[21, 2]. Being a DNA virus (Higher stability compared to RNA virus), monkeypox is less subjected to change in its genetic material (Singhal *et al.*, 2022)^[19]. An outbreak of monkeypox was first documented in 1958 after monkeys imported from Singapore became ill at a Danish research facility (Cho and Wanner, 1973)^[9]. It wasn't until 1970 that the first confirmed case of monkeypox in humans was reported in the Democratic Republic of Congo in a suspicion of a nine-month-old child having smallpox (Ladnyj *et al.*, 1972)^[14]. A Monkeypox virus consists of two clades, Western Africa and Congo Basin. The latter clade is associated with a higher rate of mortality, higher morbidity, and more transmission between humans (McCullum, 2014; Mauldin, 2022)^[18, 16]. Recently, the clades have been renamed by applying Roman numerals for the clade and lowercase letters for the subclade (WHO, 2022)^[22]. In WHO's long-term vision of the world, the Congo Basin or Central African clade is now referred to as clade I, and the West African clade is known as clade II. In clade I, virulence is attributed to its ability to inhibit activation of T cells via blocking T cell receptors and also prevents the synthesis of inflammatory cytokines such as IFN- γ and TNF- α by human cells (CDC, 2022; Chang and Metz, 1976)^[7, 8]. As well as having a gene that inhibits complement enzymes, the Central African clades also have an immune-modulating effect, but studies by various researchers have depicted that monkeypox does not inhibit the expression or transport of major histocompatibility complex molecules

which may explain its virulence (McCollum and Damon, 2014)^[18].

There is a cross-transmission of the disease between humans and animals (McCollum and Damon, 2014)^[18]. There are naturally occurring repositories of the virus in monkeys, squirrels, Gambian, dormice, pouched rats nonhuman mammals, and others. Infection occurs through bites and scratches, close contact, and eating incompletely cooked meat from infected animals. Humans transmit infections through large respiratory fluids, skin lesions of an infected person, direct contact, or contaminated fomites like clothes and bedding. In contrast to smallpox, where secondary infection rates ranged from 35%-88%, household contacts experienced a secondary infection rate of less than 10% (Jezek, 1988)^[12]. Sexual transmission of monkeypox is unclear, but intimate skin and mucosal contact during sex are likely to facilitate the spread of the disease. It has also been reported by Mbala, 2017^[17] that the inborn Monkeypox virus can also be transmitted from mother to fetus or newborn.

Epidemiology

From the year 1970 to 1986, 10 cases of human monkeypox were reported from Western African countries such as Nigeria, Sierra Leone, Liberia and Côte d'Ivoire and 394 prevalent cases were recorded from the Congo Basin countries of Cameroon, Democratic Republic of the Congo (DRC) and Central African Republic (Jezek & Fenner, 1988)^[12]. Western Africa discloses less severe disease and fewer human to human transmissions than the DRC (Ladnyj *et al.*, 1972; Foster *et al.*, 1972; Breman *et al.*, 1980)^[14, 4], when the World Health Organization (WHO) emphasized its supervision from 1981 to 1986. As claimed by the Centers for Disease Control and Prevention (CDC), the first cases of monkeypox outside of Africa were reported in 2003 where the West African clade prevailed when 53 people (median age 26 years, spanning between 4–53 years) came into interaction with pet prairie dogs, which were themselves contaminated with exotic primates from Ghana. In 2005, Sudan became the second country outside of the West African and Congo Basin region to experience monkeypox outbreaks (Brown and Leggat, 2016)^[5]. It was the first time in 39 years that 122 cases had been reported in Nigeria in 2017, indicating zoonotic transmission as well as human-to-human transmission (Heymann and Simpson, 2021)^[11]. There have been a handful of cases reported without a fatality in some countries between 2018 and 2021 (one in Israel, one in Singapore, five in the UK and Nigerian travelers returning home) (Bunge *et al.*, 2022; Alder *et al.*, 2022)^[6, 1] and the most recent cases were reported in 2022. Outside of African regions where monkeypox is endemic, human infections with the monkeypox virus were rare before May 2022. A traveller who had returned from Nigeria reported monkeypox in the UK on the 6th May 2022 (Mahase, 2022)^[15]. Since then, people without prior travel history to endemic areas have been diagnosed with cases exponentially. A number of cases are occurring across the globe at the moment. In a recent study conducted by Thornhill *et al.* 2022^[20], to investigate the

Monkeypox Virus contamination in Humans from April 27 to June 24, 2022, reported that 528 infections were diagnosed at 43 sites in 16 countries. In India, the initial case of MPX was diagnosed on July 14, 2022 when a 34 year male returned to Kerala from UAE and died on July 30. Since then, there is a total of 9 cases from Delhi (4) and Kerala (5) region and globally, more than 64,000 cases have been reported by 23 September 2022 in 107 countries. Monkeypox has re-emerged in both endemic and non-endemic areas for several reasons, including changing biology, climate change, increased deforestation, civil unrest and poverty, halting of smallpox vaccination, increased global travel since COVID-19 restrictions lifting, and unprotected sexual act. (Alakunle and Okeke, 2022).

Clinical Features

The clinical symptoms of monkey pox virus is less or more similar to other pox virus infections such as smallpox and chickenpox virus (Table 1). The virus progression has been arranged into four stages/periods. After the contact with the virus, the virus accompanies with usually 5 to 21 days of incubation period, but typically it incubates for 6 to 13 days. Although the probability of infection was equal for the all ages but the median age was the most affected. (Bunge *et al.*, 2022)^[6]. Following this comes the Febrile stage of 1- 4 days characterized by symptoms like fever, swollen lymph nodes (lymphadenopathy), headaches, chills, sore throat, malaise, fatigue etc. prevail. There may appear small lesions in the mouth (enanthem) towards the end. Within two to four weeks, lesions can be seen spreading from the face to the arms, legs, palms, and soles of the infected person (centrifugal distribution) following a specific progression pattern (Figure 1). Macules (flat, distinct, discolored areas of skin) are the first lesions followed by papules (elevated rigid or cystic spot on the skin), vesicles (superficial blisters filled with clear fluid), pustules (small, inflamed pus-filled sores), and then dried scabs (rough elevated areas with dried crust). The scabs remain on the skin for a week before falling off, and recovery takes a few days or weeks to resolve. Monkeypox virus infection starts with similar signs and symptoms as smallpox; however, unlike smallpox, lymphadenopathy occurs in 84% of patients without vaccination, and in 54% of patients with vaccination. This lymphadenopathy is tender in the maxillary, cervical and inguinal areas. (Heymann and Simpson, 2021; McCollum and Damon, 2014)^[11, 18]. Another characteristics clinical feature of monkeypox virus is appearance of lesions on the palm of the hand and sole of the foot which is usually not seen in case of smallpox or chicken pox virus. However, there are various complications from monkeypox such as corneal infection, vision loss, secondary bacterial infections, abscess and airway destruction, reduced skin pigmentation, scarring, Pneumonia, sepsis, encephalitis (inflammation of the brain), in case of pregnancy it may lead to miscarriage and in extreme cases can even cause death. Historically, the fatality ratio of monkey pox varies from 0% to 11% in population and shows higher ratio in case of young children. The present scenario of fatality ratio is 3-6% (WHO, 2022)^[22].



Fig 1: Different Stages of monkeypox lesions

Table 1: Comparison of clinical features between human monkeypox, smallpox, and chickenpox (modified from Breman and Henderson, 2002)^[4]

Disease characteristics	Monkeypox	Smallpox	Chickenpox
History			
Exposure with exotic animal	Yes	No	No
Contact to patient with vesicular rash	Possible	Yes	Yes
Vaccination against smallpox	10–15%	Rare	Yes
Incubation period (days)	6–13	10–14	14–16
Early signs and symptoms appearance (days)	1–3	2–4	0–2
Physical examination			
Early fever and malaise	Yes	Yes	Yes (mild)
Lymphadenopathy	Yes	No	No
Skin lesions distribution	Centrifugal (80%) or centripetal (5%)	Centrifugal	Centripetal
Skin lesions depth	Superficial	Deep	Superficial
Evolution of skin lesions	Monomorphic (80%) or pleiomorphic (20%)	Monomorphic	Pleiomorphic
Peeling of skin	22–24 days	14–21 days	6–14 days
Lesions on palms and soles	Common	Common	Rare
Extracutaneous manifestations			
Secondary skin/soft-tissue infection	19%	Possible	Possible
Pneumonitis	12%	Possible	3–16%
Ocular complications	4–5%	5–9%	No
Encephalitis	<1%	<1%	<1%
Laboratory diagnosis			
DNA detection (PCR)	Monkey Pox Virus	Variola virus	Varicella zoster virus.
Electron microscopy	Poxvirus particles	Poxvirus particles	Herpesvirus
chick chorioallantois Culture	Characteristic pocks	Characteristic pocks	No growth
Serology	Orthopoxvirus and MPV antibodies	Orthopoxvirus and variola virus antibodies	Varicella antibodies

Laboratory Diagnosis

Diagnostic methods of monkeypox virus includes isolation of the virus, tissue immunohistochemistry, electron microscopy,

molecular diagnosing, and serology. The genetic tests include restriction-fragment-length polymorphism (RFLP) Real Time-PCR, recombinase polymerase amplification (RPA), etc. First

and foremost, RT-PCR should be performed as a diagnostic method. The test samples collected from skin lesions, blood, throat, and urine can be used for diagnosis of the Monkeypox

virus with good sensitivity and specificity. After the negative result of the PCR test, if the infection is still suspected, other tests mentioned in Table 2 can be performed.

Table 2: Diagnostic tests for monkeypox virus

Tests	Description	Sample used
Viral Culture	Virus isolated from the patient is cultured on preferred media.	Fluid from lesions
RT-PCR	It is based on Nucleic Acid Amplification Test; for the detection of monkeypox DNA.	Fluid from lesions
Electron Microscopy	Identification of lesions morphologically	Biopsy specimen, scab material, lesions fluid
Serology (Anti-Orthopoxvirus IgG and IgM test)	Assessment of latest or remote exposure to the orthopoxvirus	Blood sample
Immunohistochemistry	Orthopoxvirus specific antigens detection	Specimens from a biopsy

The Ministry of Health and Family Welfare, Government of India has released guidelines for the administration of monkeypox disease mentioning Diagnostic modal for monkeypox. The patient samples (Lesions fluid, urine, serum, nasopharyngeal or oropharyngeal swabs) can be examined by using PCR specific for orthopoxvirus genera (Cowpox, buffalopox, camelpox, monkeypox). If tested positive, then the sample will be further examined specifically for monkeypox DNA.

Treatment

Vaccination in combination with a surveillance program can help to overcome the adverse effect of the monkeypox virus at the global level. However, monkeypox lacks a specific treatment at the moment. Patients suffering from the virus can be benefitted from supportive care and medications incorporating maintaining fluid and electrolyte stability, nourishment, antipyretics for fever, analgesics to alleviate pain, identifying secondary infections early, and treatment with appropriate antibiotics. As per WHO 2022^[22], patients with severe infection, immunocompromised patients, pregnant women and the pediatric age group requires specific treatment. Rehydration therapy and nutritional support is important to prevent dehydration by encouraging ORS or oral fluids and intravenous fluid when required. Monkey pox virus shares similarities with smallpox virus, so the drugs and vaccine initially equipped for smallpox treatment shows positive signs of potency against the monkeypox virus (Brown and Leggat, 2016)^[5]. Tecovirimat, an antiviral drug used in the treatment of smallpox has been approved by FDA and the European Medicines Agency (EMA) in 2022 based on its primates trials (WHO, 2022)^[22]. The dosage of Tecovirimat is available as oral capsules containing 200 mg of tecovirimat active ingredient taken with a full glass of water within 30 minutes of having meals and injection vials of 200 mg/ 20 mL administrated to the patients accordingly. The total duration of tecovirimat for patients of all ages is 14 days but may alter depending upon the progression of the disease and the clinical condition of the patient (CDC, 2022)^[7]. Another medication named Brincidofovir (Tembeva) which is an antiviral drug was licensed by FDA on June 4, 2021 for treating the smallpox virus in adults and children including newborns. It has shown effectiveness against the orthopox virus in *in vitro* studies. A similar drug named Cidofovir (Vistide) which is a broad-spectrum antiviral drug has proved its potential against orthopox virus and CDC also accessed the use of cidofovir for the treatment of the orthopox virus outbreak.

Vaccination against smallpox (Vaccinia) has proven to be 85% effective against the monkeypox virus. The US CDC has allowed the use of Vaccinia Immune Globulin Intravenous (VIGIV) which is an immunoglobulin required to treat

problems from vaccinia immunization as a treatment for monkeypox. With advancements in medicine and technology, the Ankara strain of vaccinia virus, which uses attenuated vaccinia virus DNA, has been approved as a monkeypox vaccine in 2019. Recently, Food and Drug Administration (FDA) has accepted the smallpox/monkeypox vaccine (JYNNEOS) made by weekend live vaccinia virus and has proven not to cause smallpox, monkey pox or any other infectious disease in adults of 18 years or older. The vaccine should be administered as a series of 2 injections, 4 weeks apart.

Prevention

The crucial intrusions to avoid a monkeypox outbreak includes a high index of suspicion, recognition of symptoms fast, isolation of the infected individual, contact tracing and stern infection prevention applications by healthcare individuals (Di Giulio and Eckburg, 2004; CDC, 2022)^[10, 7]. Spreading awareness of the risk factors of the monkeypox virus and instructing people about the preventive measures taken to decrease exposure to the virus is one of the prevalent strategies for the prevention of monkeypox. Inspection and swift recognition of the latest cases are censorious for monkeypox outbreaks. A patient with suspected or validated monkey pox contamination should be isolated with proper precautions. To minimize the risk of contact with others, patients should use a triple-layer mask and cover their skin lesions with approximate possible by wearing pants and long sleeves. The isolation period should last until the scabs have been completely fallen off (WHO, 2022)^[22]. Health workers, household members and person who was in acquaintance with the contaminated person are at a high risk of infection. PPE (Disposable gowns, gloves, eye goggles, N95 masks) should be used by healthcare people and the patient contacts before entering the patient's room. Suitable precautions drawn for the administration of waste which includes handling, treatment, storage and disposal of used PPE, patient dressing, bedding, proper hygiene etc. Specimens drawn from the suspected individuals and animals should be handled by instructed staff members at a properly equipped laboratory. Moreover, contact monitoring should be persuade for further outbreak. The healthcare workforce and contacts of patients who have had an exposure to the monkeypox virus ought to be isolated and observed for the onset of indicting symptoms for a period of 21 days from the last contact with the patient. Blood, cells, tissues, organs, and semen should not be donated by asymptomatic contacts when they are under surveillance (WHO, 2022)^[22].

One of the primary causes of monkeypox outbreaks is animal-to-human transmission. Interaction with wild animals especially those dead or unwell incorporating their meat, blood or other parts should be avoided. Moreover, the meat should be

cooked properly before consumption. In addition to these factors, the import of animals from the endemic area should be restricted. The captive animal that has been contaminated with the monkeypox virus ought to be immediately isolated and placed into quarantine. Animals suspected should be directed for standard precautions and noticed for any symptoms in the next 30 days.

Conclusion

It is admissible that various countries have accepted monkeypox cases since May 2022 with no progressed links to particular areas. The WHO has declared the monkeypox virus to be a Public Health Emergency of International Concern (PHEIC) by July 2022. The virus is spreading at the current moment and with limited clinicians, unavailable diagnostic facilities, and undefined treatment and therapeutics the chances of its outspread is very high. Greater insight into various factors influencing the spread will help in ensuring public health, and hygiene and advancing strategies in opposition to the foreseeable threats.

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