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A recap of monkey pox virus: Its threat and implications

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Abstract
The world has faced disease challenges with pandemic disease (COVID 19) and people are still under the fear of corona viral disease. Before it settles down, now the world is facing another endemic challenge with the Monkey Pox outbreak in 2022 especially in non- endemic countries including India. Animal to human transmission is possible by direct contact with infected animals either by bites or scratches or respiratory droplets or food from bush meat or handling other animal products. In the context of re-creating an awareness about the importance of monkey pox and the threat it can cause is being recapped in this review article.

Keywords: MPX, genome, zoonoses, transmission, pathogenesis, vaccines

Introduction
Monkey pox (MPX) virus is a zoonotic agent and closely related to the similar symptoms caused by small pox virus. Due to the termination of smallpox vaccine administration could be the reason monkeypox cases became more prevalent (Bunge *et al*., 2022 and Kaler, *et al.* 2022) [2]. Because small pox vaccine provided cross immunity with > 85% protection against Monkey pox (Fine *et al*., 1998) [3].
MPX was first discovered in 1958 from Cynomolgus monkeys kept for research at a Danish laboratory (Magnus *et al*., 1959) [4], hence the name arrived as 'monkeypox'. The first human case of monkey pox was reported from Democratic Republic of the Congo (later was called as Republic of Zaire) in 1970 in nine month old boy and DRC continues to report the majority of cases each year (Ladnyj *et al.*, 1972) [5], mainly in children under 10 years and its thought that MPX was restricted only in African countries. First report outside Africa was reported in 2003 in the United States of America. African mammals were shipped from Ghana into Texas. Amongst the shipment were three rope squirrels, two giant pouched rats, and nine dormice infected with MPX (Hutson *et al.*, 2007) [6].
In the period between 1st January 2022 and 22nd July 2022, 16,016 laboratory confrmed cases of monkeypox and 5 deaths have been reported to World Health organization (WHO) from 75 countries/territories (WHO. 2022a)[7]. On 15th July 2022, WHO news release reported the first case of monkeypox in South-East Asia Region and has been reported from India, in a 35-year old man who arrived from the Middle East and one death recorded from Kerala (Unpublished data).

Etiology
Monkey pox virus (MPXV) is a double stranded enveloped virus belonging to the family Poxviridae, genus Orthopoxvirus. The other members in this genus are variola virus (VARV), monkeypox virus (MPXV), cowpox virus (CPXV), and vaccinia virus (VACV). (Moss, 2001)[13].They are typically brick-shaped with an irregular surface of projecting tubular or globular structures. The viral nucleocapsid has complex symmetry with a dumbbell-shaped core that contains the viral DNA, together with several proteins, two lateral bodies, outer membrane, and sometimes an envelope. Virions are released by budding, and have an extra envelope in many cases. The envelope is derived from golgi apparatus. Unlike other DNA viruses, poxviruses encode all of the enzymes required for transcription and replication (Fanner).
Two genetic clades of Monkeypox virus have been characterized including the West African and the Central African clade (Congo basin Clade).

The West African clade shows the mortality rate of < 1% and there is no documented transmission from human to human. But Congo basin clade showed 11% mortality rate with human to human transmission (Jezek, *et al*., 1987 [9]. There is a virulence difference in Central African strain and West African strain having a 0.55-0.56% nucleotide difference between the two strains (Chen *et al*. 2005) [10]. The newly affected countries during recent outbreak in 2022 belongs to West African clade (WHO, 2022c) [11].

The genomes of monkeypox and variola viruses differ in the terminal region and 96% similar in the central region. The terminal regions the place where most of the virulence and host-range genes are located Phylogenetic analysis has shown that the variola and monkeypox viruses have a common ancestor but have not evolved one from the other (Chen *et al*. 2005; 10]. Genes with known function present in monkeypox virus are absent/ fragmented in variola virus (Weaver and Isaacs, 2008) [12].

Molecular evidences of MPXV

MPXV is linear genome of approximately 197kb in size (Moss, 2001; Hendrickson *et al*., 2010) [13, 14]. Highly conserved central coding region and end with variable inverted terminal repeats containing non- conserved genes are species and host specific (Moss 2001; Gong *et al*., 2022) [13, 15]. MPXV contains at least 4 ORFs in the ITR region but variola virus lack ORF in ITR region Hendrickson, *et al*., 2010) [14].

MPXV encodes a variety of host range proteins, such as the virulence protein BR203 virlence protein, which exerts antiviral-infected apoptosis effects (Barry *et al*., 1997; Hnatiuk, *et al*., 1999) [16, 17]. BR-209 protein is an IL-1β-binding protein that inhibits IL-1β and IL-1 receptor binding (Alcami, *et al*., 1992; Spriggs, *et al*., 1992) [18, 19]. BR203 gene play a role in MPX virulence but not required for small pox virulence and above mentioned two proteins are not present in small pox virus (Weaver and Isaacs, 2008)[12].The other proteins are involved in inhibiting cellular antiviral immune response are MPXV F3 (Arndt *et al*., 2015) [20].

Natural reservoir for monkey pox is still unknown, reports suggest that as like human as incidental host, monkeys are also the incidental host. However, certain rodents (including rope squirrels, tree squirrels, Gambian pouched rats, dormice) are the reservoir host (Nalca, *et al*., 2005) [21].

Transmission

1. Animal to human transmission is possible by direct contact with infected animals either by bites or scratches or respiratory droplets or food from bush meat or handling other animal products. People living in or near to forest are also prone to exposure to infected animals (WHO, 2022d) [22].
2. Human to human transmission by direct contact with infected person like respiratory secretion or through rashes or scab material or through sexual contact (WHO, 2022d) [22]. In the recent outbreak 2022, in the United states 99% of cases were among men, among this 94% reported male-to-male sexual contact
3. Trans placental transmission from mother to fetus through placenta leads to congenital monkey pox (WHO, 2022d) [22].
4. Human to animal transmission (reverse zoonoses) documented a first report of monkey pox transmission from human to pet dog (male Italian greyhound) by close contact in France (Sophie *et al*., 2022) [24].

Pathogenesis

Through the site of viral entry (either through direct or indirect contact) the virus multiply in the respiratory or oral mucous membrane and then spreads to local lymph nodes leads to primary viremia. Then virus spreads to regional lymphnodes and other organs. Prominent symptoms will not be evinced during the incubation period and the person who are in the incubation period will not spread the disease from one person to other (Moore and Zahra 2022; Kaler 2022) [25, 2].

Clinical presentation

Humans: The incubation period has been estimated at 5 to 21 days (WHO, 2022d) [22]. Clinical signs can be exibibited as prodromal or invasion period which persist for 0-5 days starts with non-specific symptoms like fever, myalgia, back pain, asthenia (lack of energy) and lymphadenopathy (lymphnodes of neck, axilla, groin) (WHO, 2022d; Gomez-Lucia, 2022) [27, 22]. Lymphadenopathy will not be seen in small pox or chicken pox (Nalca, *et al*., 2005) [21]. In this prodromal period the affected person is more infectious (Kaler 2022) [2]. Next the skin eruption/rashes starts appearing within 1-3days of fever.

The virus has the affinity for the epithelial cells especially the stratum spinosum. In the previous outbreak the lesion are itchy mainly restricted with face, palms and toes (Gomez-Lucia., 2022) [27]. But now in 2022 multi countries outbreak they are mostly in the genitalia or perineal region and donot spread further (WHO. 2022d; Gomez-Lucia., 2022) [22, 27]. The sequence of events as follows, during the 2-3 weeks period initially starts with macule (lesion appear on face moves to periphery especially to palms and toes), papule, vesicles each lesion persist for 1- 2 days, pustules (5-7 days), and then crust or scab formation. Once the scab get sloughed off, the affected person is no more contagious (Kaler 2022) [2]. This lesion can also be noticed in the mouth, tougue causing difficulty in eating leading to dehydration and also in the genitalia (Nalca, *et al*., 2005) [21].

The most important and serious complication is ocular infection causing corneal scarring and blindness (Kaler 2022) [2]. Monkey pox is a self-limiting disease with symptoms lasting for 2- 3 weeks. Historically mortality was 11% and more death among children's, but in recent multi countries outbreak 2022 case fatality is 3-6% and mortality are more evinced during second week of disease (Nalca, *et al*., 2005; WHO 2022d) [21, 22].

Animals

In non-human primates especially monkeys no non- specific symptoms of illness will be seen as like in humans but rarely with oedema of face starting from the bridge of nose. The cutaneous lesion are multiple, shot like papules seen over the entire trunk and tail but more concentrated in the extremities of limbs (Arita and Henderson; 1968) [28]. Mortality is rare but can occur in young monkeys. In rabbits, rodents, prairie dogs, starts with non-specific symptoms including fever, cough, reddened nose, swollen glands. After that starts with cutaneous lesion include fever, small swellings, containing pus ("pocks"), and patchy hair loss can develop. (CFSPH, 2013) [29].

Diagnosis

a. **Sample collection:** dry swabs of lesion material, swabs from lesion in viral transport media, scab/crust, vesicular fluid. Swabs has to be taken from two different location and cotton swab has to be avoided (CDC, 2022b) [30]. Scab material and vesicular fluid should not be mixed together. Apart from this or pharyngeal swabs can also be collected. Specimens suspected for monkey pox should be refrigerated (2-8°C) or frozen (-20 °C or lower) within one hour after collection (WHO, 2022e) [31].
b. **Antibody detection:** Serum antibodies (IgM and IgG) can be detected within 5 days and more than 8 days after the rashes development. Cross reaction with other orthopoxviruses sets up a limitation for immunological assays. But still IgM ELISA detects recent infection in orthopoxviruses suspected for monkey pox either in vaccinated or natural infection, (Karem, *et al*., 2005) [32]. Detection of IgM or IgG antibodies in the sample is a clear indication of recent or previous infection with orthopoxviruses (Alakunle, *et al*., 2020) [33].
c. **Antigen detection:** Immunohistochemistry is used to differentiate between orthopoxviruses infection and herpes virus. Electron microscopy can identify the virus based on its morphology (Alakunle, *et al*., 2020) [33].
d. **Virus isolation:** Adaptation of the virus in vero cells produced typical cytopathic effect of cell rounding and monolayer separation with viral factories within 24 hrs specific for poxviruses (Shchelkunov, *et al*., 2005) [34].
e. **Molecular detection:** The genome of orthopox virus and monkey pox virus are very similar (>90%) (Li, *et al*., 2007) [36] and there is a dire need of molecular diagnosis for detection of monkey pox. The types of molecular assays for diagnosis is as follows.

- **Multiplex PCR:** Species specific primers to differentiate the members of orthopoxviruses along with specific primers to differentiate the two clades (West African and central African) of monkeypox (Shchelkunov, *et al*., 2005) [34].
- **Real time PCR:** (q-PCR) targeting two genes, the DNA polymerase (E9L) and envelope protein (B6R). E9L detect orthopoxviruses other than variola virus and not able to make species specific identification. Yet another gene is envelope protein (B6R) detects only the monkey poxviruses. These assays are highly sensitive and specific (Li *et al*., 2006) [35]. Apart from this, to differentiate two clades of monkey pox viruses, TNF receptor gene is used to detect West African strain and C3L gene to identify Congo Basin strain (Li, *et al*., 2010) [37] by real time PCR.
- **Whole genome sequencing:** Monkey pox genome can be characterized by whole genome sequencing which is considered as a gold standard method for characterization (Alakunle, *et al*., 2020) [33]. Nowadays q-pCR and sequencing are important tools for identifying species specific monkey pox virus differentiating it from other orthopox viruses. With certain limitation third generation sequencing has made it possible for clading monkey pox strain utilizing Oxford Nano pore technologies (ONT).

Prevention

1. Personal protection

- Affected person has to be isolated till the crust slough off
- Avoid close contact with infected person
- Avoid using/touching in animate objects (clothing, bedding) used by the infected person.
- Frequent washing of hands with soap and water after touching or shaking hand with affected person.
- Wearing of three layered mask.
- Avoid eating improperly cooked bush meat.
- The care takers for the affected person has to wear proper personal protective equipment (PPE).
- Care should be taken while handling laundry (e.g., bedding, towels, and clothing).
- Laundry may be washed with warm water and detergent. (Adapted from GOI, 2022).

2. Vaccines

The value added thing in smallpox vaccine is that it provides cross protective immunity against all other orthopoxviruses. With certain adverse effect and risk factors associated with first and second generation live small pox vaccine, these drawbacks made platforms for the development of third generation small pox vaccine with less side effects when comparing the previous generation small pox vaccine. The third generation small pox vaccine are Imvamune/ Imvanex/JYNNEOS which was licensed in 2019 by the U.S. Food and Drug Administration (FDA) for the prevention of *Monkeypox virus* infection and small pox infection. It is live (replication defective) modified vaccinia Ankara vaccine and chicken embryo fibroblast adapted vaccine. CDC recommends that this vaccine can also use in immunosuppressed patients like HIV/Pregnancy safe (Petersen *et al*., 2015; CDC, 2022c) [42]. ACAM 2000, licensed by FDA for use against smallpox is made available for use against monkey pox disease.

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