

Monkeypox: epidemiology, mode of transmission, clinical features, genetic clades and molecular properties

S. KANNAN, P. SHAIK SYED ALI, A. SHEEZA

School of Medicine, The Maldives National University, Male', Maldives

S. Kannan and P. Shaik Syed Ali equally contributed as first authors

Abstract. – OBJECTIVE: Recently monkeypox cases have been reported from many non-endemic countries. The objective of this article is to bring out the epidemiology, mode of transmission, clinical features, genetic clades, and molecular properties of monkeypox virus.

MATERIALS AND METHODS: A detailed literature review was conducted on monkeypox, using databases PubMed/Medline, EMBASE, PMC and Cochrane Library, for the period between 1985 to 2022.

RESULTS: Genetically monkeypox virus can be classified into Central African clade and Western African clades. The sequence similarity between the two strains was found to be 99.5%. However, some significant differences were found in the virulent and nonvirulent genes of the strains, such as BR-203, BR-209, COP-C3L b and COP-H5R, COP-A9L, COP-A50R, and COP-A36R, respectively. Human to human transmission occurs after exposure to respiratory droplets, oral secretions, contact with lesions, fomites, and direct/sexual contact. Monkeypox can also be transmitted from the infected mother to the fetus through the placenta leading to congenital infection. In May 2022 several cases have been reported from Europe, North America, and Australia, particularly from homosexual men.

CONCLUSIONS: Monkeypox is a zoonotic disease which was prevalent in Central and Western African countries. Recently, human to human spread was noticed in developed countries of Europe, North America and Australia. Despite with a close genetic similarity between the two clades, the Central African strain is comparatively very virulent with high mortality. Monkeypox should be considered a re-emerging, neglected disease and proper measures like hand hygiene, wearing masks and vaccination to the high-risk groups are advised.

Key Words:

Monkeypox, Epidemiology, Mode of transmission, Clinical features, Molecular properties, Virulence.

Introduction

The family Poxviridae consists of poxviruses that are complex and largest viruses affecting humans and animals¹. Poxviruses includes variola, vaccinia, buffalopox, cowpox, pseudo cowpox, orf, bovine popular stomatitis, tana pox, yabapox, monkeypox and molluscum contagiosum. Monkeypox virus is subclassified under Orthopox virus genus². The morphology of all pox viruses resembles each other and possess similar nucleoprotein antigen. Infections due to these viruses are indicated by rash which is often proliferative.

Monkeypox is a zoonotic disease transmitted to humans from primates and a variety of rodents, upon direct contact. The route of entry of this virus is through cut/abrasion or mucous membranes. Several monkeypox outbreaks have been reported through human-to-human transmission³. Recent reports⁴ suggest that monkeypox can also be transmitted through sexual route. The clinical signs and symptoms of monkeypox resembles like that of smallpox caused by variola. But the severity of monkeypox is mild compared to smallpox. Monkeypox cases are rare and occurs usually in countries of Western and Central Africa⁵.

Monkeypox virion consists of complex symmetry, 400 nm x 250 nm size, brick shaped with outer irregular ridges, lateral bodies and a core with double stranded (ds) DNA as genetic material (Figure 1)⁶. Monkeypox virus comprises of two prominent genetic clans depending upon its geographical distribution. The one distributed in Congo and adjacent countries are called the Central African clan. The other prominent in Nigeria and neighboring countries are denoted as West African clan. It was observed that Central African clan is associated with aggressive disease with high transmissibility. Surprisingly in Cameroon both clades of monkeypox cases have been documented⁷.

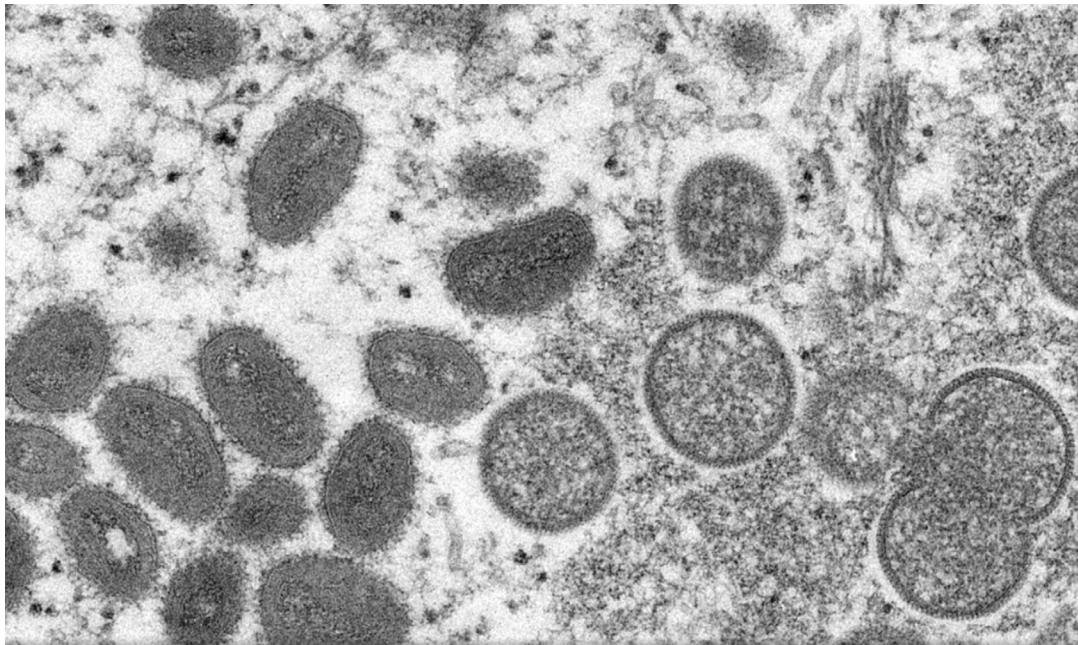


Figure 1. Electron micrograph of monkeypox virus – courtesy CDC.

Materials and Methods

The detailed literature review was conducted on monkeypox, using databases PubMed/Medline, EMBASE, PMC, Cochrane Library and UpToDate. The search was conducted on the relevant aspects of monkeypox. The inclusion criteria for this review were: (a) articles written in English; (b) articles published in the period 1980 to 2022. Articles were excluded based on the following criteria: (a) articles with insufficient data; (b) outdated and obsolete data; (c) studies prior to 1980. Further information was also obtained from gray literature.

Results

Epidemiology and Mode of Transmission

Monkeypox virus can infect a variety of wild animals and domestic animals. Some of the natural hosts include primates, dormice, wild squirrels, African pouched rodents and mongoose⁸. The exact and ideal natural reservoir for monkeypox is not discovered yet. Smallpox caused by variola major and variola minor have been eradicated by successful vaccination.

Monkeypox remains endemic in the forests of Central and Western Africa. Human cases of monkeypox were reported in USA in 2003⁹. Be-

fore 2003, the cases of monkeypox were restricted to Central and Western Africa. During the 1970s, between 1970-1979, a total of 48 confirmed cases occurred in the African subcontinent. Most number of cases occurred in Democratic Republic of Congo with at least 38 cases, 3 cases in Nigeria and 1 case each in Cameroon, Côte d'Ivoire and Liberia¹⁰. In the 1980s, between 1980-1989, 343 cases occurred in Democratic Republic of Congo that was a nine-fold increase compared to the previous decade¹¹. Additionally, 8 cases reported from Central African Republic, 4 in Gabon and 1 in Cameroon and Côte d'Ivoire¹². In the 1990s, between 1990-1999, 511 cases were detected in Democratic Republic of Congo that was 1.5 times higher than the 1980s decade. Between 2000-2009, the monkeypox occurrence cases were almost 10,027 in Democratic Republic of Congo, 73 in Congo, 19 in South Sudan and 47 in USA¹³.

The sudden jump of cases from African subcontinent to USA occurred in the year 2003. Nearly, 71 cases occurred in the Midwestern states of USA including Wisconsin (39), Indiana (16), Illinois (12), Kansas (1), Missouri (2), and Ohio (1) between May - July 2003¹⁴. The source of infection was prairie dogs that were housed with Gambian rodents imported from Ghana into USA. However, no mortality was reported in USA. Horizontal transmission was reported in Africa but not in USA. All the monkeypox cas-

es reported in USA Midwest were the result of direct contact with prairie dogs⁴. Between 2010-2019, the monkeypox cases were as follows, Democratic Republic of Congo (18,788), Nigeria (181), Central African Republic (61), Congo (24), Liberia (6), Sierra Leone (2), Israel (1), Singapore (1)¹⁵. At least 3 cases were reported in UK in the year 2017. This was the first ever case in UK/European Union (EU). The first two cases were imported from Nigeria as they travelled to Nigeria during monkeypox outbreak in Nigeria in 2017. The third case, health care assistant, occurred due to horizontal transmission from the patient¹⁶.

In Congo, first human case of monkeypox was discovered in 1970. This was identified in a young male patient with smallpox symptoms in Congo where smallpox was eradicated. Later many cases have been frequently reported in Congo and other countries of Western and Central Africa. Initially, monkeypox cases in human have been documented from the Republic of Congo, the Democratic Republic of Congo (DRC), Central African Republic, Liberia, Benin, Cameroon, Gabon, Cote d'Ivoire, Nigeria, Sierra Leone and Sudan. The disease burden of monkeypox virus is not yet identified. More human cases of monkeypox have been documented in DRC until 1997¹⁷. Later in Nigeria hundreds of cases have been recorded from 2017 until today with moderate to severe complications. The case fatality ratio observed in Nigeria outbreak was 3%¹⁸.

Human to human transfer of monkeypox virus can arise after very close/intimate contact, oral/respiratory secretions, droplets, skin lesions or through contaminated fomites. Surprisingly, it was observed that congenital transmission through placenta from infected mother to the fetus was documented. This is called 'congenital monkeypox' suggesting that monkeypox virus can surpass placental barrier. This may result in the developmental anomaly of the fetus¹⁹.

In 2018 in Israel, travelers from Nigeria have been infected with monkeypox virus²⁰. Nigerian travelers to the UK in 2018, 2019, 2021 and May 2022 were affected by monkeypox virus. Passengers from Nigeria in the year 2019 carried this virus to Singapore. Nigerian travelers also harbored monkeypox virus when they landed in USA in the year 2021²¹.

Recently, in May 2022, several cases of monkeypox have been registered in non-endemic countries such as, Portugal (14), Spain (7), Canada (2), Belgium (2), Italy (1), France (1), UK (9), USA (1) and Australia (1). In these countries it

was noticed that the infected patients were homosexual men. Surprisingly these patients have no recent travel history to Central or Western African countries. All these patients were isolated and quarantined and the May outbreak did not end up in any deaths so far (Epidemiological update: Monkeypox outbreak - ECDC).

Genetic Clades and Molecular Properties of Monkeypox Virus

Among the two clades of monkeypox, Central African clade is relatively more pathogenic than the Western African clade. A high fatality rate was associated with Central African clade with little to no fatality in Western African clade. Animal experiments with monkeys showed that the animals died when challenged with high doses of Central African clade strains, whereas those animals when challenged with Western African clade strains survived¹⁴.

Central African strain and Western African strain showed 99.5% nucleotide sequence similarity and 99.4% amino acid (aa) sequence similarity between them. Nearly, 56 virulent genes were discovered with 53 genes present in the strains¹⁶. Comparison of genomes showed significant differences between the Central African and Western African strains²². Some significant differences were found between the two strains in the orthologs of BR-203, BR-209, and COP-C3L b¹⁶. BR-203 encodes a 221 aa virulence protein in the Central African strain and in Western African strain as a N-terminal 51 aa protein²³. It is presumed to play a role to prevent apoptosis of infected lymphocytes²⁴. BR-209 encodes the IL-1 β -binding protein. In Central African strain BR-209 encodes the two fragments of N-terminal protein fragment of 210 aa and a C-terminal protein fragment of 126 aa. In Western African strain it encodes a N-terminal 163 aa fragment and a C-terminal 132 aa fragment. An independent study²⁵ revealed the presence of 326 aa full-length protein in Central African strain. Interleukin-1 β (IL-1 β) binding protein prevents the IL-1 β from binding to the IL-1 receptor.

COP-C3L encodes the complement control protein. The monkeypox inhibitor of complement enzymes (MOPICE) is not expressed by viruses of the West African strains but only by Central African strains. It is encoded as a 216 aa protein. It was presumed that in Central African clade, the MOPICE might be the virulence factor responsible for increased pathogenicity. With MOPICE gene knockout the viral replication was

enhanced, and the adaptive immune response was dampened. However, this is not the sole virulence factor responsible for pathogenesis²⁶. The presence of MOPICE, full length protein or a longer version of N-terminal IL-1 β -binding protein and a longer version of N-terminal virulence protein might be responsible for enhanced pathogenesis of Central African strain. Some additional differences were found between the Western African and Central African strains nonvirulent genes that influence the replication and transcription of monkeypox virus. The difference in sequence of genes were found in COP-H5R (late transcription factor), COP-A9L (morphogenesis factor), COP-A50R (DNA ligase), and COP-A36R (role in actin tail formation)¹⁵.

Clinical Features of Monkeypox

The signs and symptoms of monkeypox resembles to an altered type of variola (smallpox) (Figure 2). Cropping rash caused by monkeypox virus is similar to varicella (chickenpox), this may hinder the clinical diagnosis of monkeypox patients (Figure 3)².

The incubation period of monkeypox virus is approximately 2-3 weeks. The monkeypox infection can be divided into two phases, the invasion period and the skin eruption phase. Invasion phase is the first phase that starts in the first week with lymphadenopathy, fever, arthralgia, myalgia, and severe asthenia. In smallpox, measles and chickenpox lymphadenopathy is absent. The skin eruption phase starts after fever with rashes found more on face and extremities and mildly on the trunk. In most of the cases, face is affect-

ed followed by soles, palms, oral cavity, genitals, cornea and conjunctiva. The rash of monkeypox emerge sequentially from macules to papules, vesicles, pustules and crusts. Single patient infected by monkeypox virus may have several thousands of lesions in the body (Figure 4). Normally, monkeypox infection will resolve on its own within 3-4 weeks (Figure 5). Most commonly children are prone to acquire the infection. Underlying disease and immune status may determine the severity and mortality of monkeypox¹³. In many patients infected with monkeypox virus may elicit severe and fatal complications. It may range from serious lung infection (after secondary bacterial invasion) to CNS complications. Infection can lead to sepsis, pneumonia and loss of vision due to corneal scarring. It can also spread to other vital organs in the body leading to death. The clinical signs, disease course and complications observed in the year 1970 and later decades is similar to the recent monkeypox outbreak in 2022¹⁴. This may be attributed to its stable nature of viral DNA genome that do not easily undergo significant mutations over a period of time, unlike RNA viruses²⁷.

Discussion

The difference observed between the old monkeypox cases and the recent monkeypox mainly lie in the mode of acquisition, all other aspects remain the same. Recent monkeypox cases outbreak in Europe included sexual transmission too apart from other modes of transmission. Monkeypox cases were observed predominantly in homo-



Figure 2. African child with lesions of monkeypox – courtesy CDC.



Figure 3. Scabs of monkeypox on the palms – courtesy CDC.

sexual and bisexual men due to the appearance of lesions in the genital and anal areas and the virus ability to transmit through intimate close contact^{14,28,29}.

Since the nucleoprotein of vaccinia virus is antigenically similar to smallpox and monkeypox, vaccination against vaccinia can protect monkeypox. It is calculated that the mortality rate of monkeypox in non-vaccinated individuals may go beyond 10%. Recent research established that vaccination with vaccinia also reduces the severity of monkeypox. But vaccination with vaccinia to prevent smallpox was already discontinued throughout the world after its eradication. This is the main reason that led to the surge and emergence of human monkeypox cases in African and non-endemic countries¹⁴.

In the early times, the monkeypox diagnosis was conducted mainly by physical examination, clinical signs and symptoms. Nowadays modern techniques like polymerase chain reaction (PCR), real time polymerase chain reaction (RT-PCR), Immunofluorescent technique (IFT), cell culture and electron microscopy with negative staining are employed⁹.

Conclusions

Monkeypox is a zoonotic disease which was prevalent in Central and Western African countries spread to developed countries of Europe, North America and Australia in the last two decades. Monkeypox is similar to smallpox on ba-



Figure 4. Different stages of lesions of monkeypox – courtesy CDC.



Figure 5. Monkeypox patient showing resolving lesions on the dorsal surfaces of the hands – courtesy PHIL-CDC.

sis of genetics and antigens, so vaccination with vaccinia can prevent monkeypox or reduce the severity of the disease. Monkeypox can cause severe life-threatening disease. The mode of transmission is by various ways such as from animals, direct/sexual contact, respiratory secretions or through the active lesions. Despite with 99.5% genetic similarity between the Western African and Central African strains, the Central African strain is comparatively very virulent with high mortality. To conclude monkeypox should be considered as a reemerging disease. It is necessary to prevent this disease by vaccination using vaccinia. Precautionary measures like hand hygiene and the use of mask are very vital to prevent the spread.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Informed Consent

Ethical guidelines are duly followed for informed consent as per the declaration of Helsinki.

Authors' Contributions

Kannan Subbaram conceptualized to the development of the article. Shaik Syed Ali. P involved in the preparation of the article. Sheeza Ali contributed to data analysis, interpretation and preparation of the manuscript.

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ORCID ID

Kannan Subbaram: 0000-0001-8547-0957
Shaik Syed Ali. P: 0000-0002-5764-665X
Sheeza Ali: 0000-0002-0248-6628

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