Monkeypox Virus: Transmission, Signs and Symptoms, Prevention, and Epidemiology

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ABSTRACT

Monkeypox virus causes a zoonotic disease that is similar to smallpox-like illness. This review focuses on the overall epidemiology of monkeypox infection along with the transmission, signs and symptoms, treatment and prevention of the infection among humans. The early symptoms of the infection are flu-like and include fever, malaise, headache, papulopustular rash, sore throat and enlarged lymph nodes. Previously, it was reported in African countries only, with majority of the reported cases in Democratic Republic of Congo (DRC). Later in 2003, the first case of monkeypox infection was reported outside Africa in the U.S. with additional cases in the UK, Israel and Singapore. The transmission of monkeypox virus occurs primarily from animal to human and secondarily from human to human by contact with respiratory secretions or lesions of infected persons. Moreover, monkeypox virus can also be transmitted sexually from male to male and results in rashes and lesions around the genital or anal area of the infected person. Currently, there is no specific treatment for monkeypox infection. However, anti-viral treatment for smallpox, cytomegalovirus retinitis in AIDS patients, and the vaccine vaccinia virus intravenous immunoglobulins are the choice of therapeutics for treating the infection. This review focuses on the overall epidemiology of monkeypox infection along with the transmission, signs and symptoms, treatment and prevention of the infection among humans.

Keywords: Anti-viral Treatment, Central-African Clade, Cidofovir and Vaccinia Immune Globulin Intravenous, Cidofovir Therapy, Cidofovir Treatment, Congo Basin Clade, Epidemiology of Monkeypox, Immune Vaccine, Imvanex Vaccine, JYNNEOS, Monkeypox, Orthopoxvirus, Pox-Like Diseases, Poxviridae, Sexually-Transmitted Diseases, Smallpox-Like Diseases, STD, Sexually-transmitted Infection, STI, Tecovirimat, Variola, VIGIV, Viral Exanthema, West-African Clade, Zoonotic Disease.

I. INTRODUCTION

Monkeypox is a zoonotic viral disease caused by monkeypox virus belonging to the genus Orthopoxvirus in Poxviridae family [1]. Other viruses in this genus include cowpox virus, vaccinia virus and variola virus. The virus can be transmitted to humans by means of various routes like skin, mucous membrane and respiratory tract, and various sources like humans, non-human primates, and rodents [2].

Monkeypox virus was discovered for the first time in 1958 when it caused two outbreaks in colonies of monkeys that were kept for research. The virus was named as 'monkeypox' because of the pox-like disease, it caused in monkeys. It was discovered in humans for the first time in 1970 in Africa. Later, it spread to other African and non-African countries like Singapore, U.K., Israel, and U.S. The spread of monkeypox in these countries was majorly linked to imported animals like African rodents or international travel. The largest number of monkeypox infection cases were recorded in the Democratic Republic of the Congo [3].

Genetically, 2 clades of monkeypox virus have been determined namely the Central African clade/the Congo Basin clade and the West African clade. Both the clades are separated geographically and have different clinical and epidemiological features. The isolates of the Central African clades were originated from Cameroon, Democratic Republic of Congo (DRC), Gabon, Central African Republic, and Sudan [4], while the isolates of the West African clade were isolated from outbreaks in Liberia, Sierra Leone, USA, Ivory Coast and Nigeria. In comparison, the case fatality rate (CFR) for the Central African clade (up to 11%) is higher than that of the West African clade (less than 1%). In light of the available data, it is observed that the Central African clade is more common, and endemic as compared to that of the West African clade as every year more than 2000 suspected cases of this clade are reported in the DRC [5].

With the rise of monkeypox infection cases recently in the U.S. and other countries, there is a need for detailed investigation of the clinical manifestations and course of disease to better inform the scientific community about the historical context and current knowledge regarding
monkeypox infection. This review aims to provide a comprehensive picture of monkeypox infection cases from its early reports from African countries to its recent reports from non-African countries.

II. METHODS
This paper compiles data from original peer-reviewed articles and review articles regarding the detailed signs and symptoms, transmission, therapeutics, prevention, and epidemiology of the infection. Articles for this review were selected after literature search from PubMed, Scopus, and Google Scholar. We used keywords including Monkeypox virus, Monkeypox infection, Monkeypox, epidemiology of Monkeypox, clinical course of Monkeypox, transmission of Monkeypox, and treatment of Monkeypox. Furthermore, we used combination of MeSH terms to extend our literature search. Studies including only humans were selected without language restrictions. A total of 21 studies were included in this review.

III. DISCUSSION
Previously, monkeypox infection was reported mainly in African countries including DRC, Cameroon, Nigeria, and others. However, recent studies reported its spread to non-African countries due to travel history of infected persons to Nigeria. Here we describe the characteristics of monkeypox along with its modes of transmission, signs and symptoms, treatment, prevention and epidemiological characteristics in the U.S. and other countries of the world.

What is monkeypox?
Monkeypox is a sporadic, zoonotic, smallpox-like disease with viral exanthema caused by monkeypox virus. It is a double-stranded DNA enveloped virus with 2 clades. The genome size of monkeypox virus is 190 kb that is enclosed in dumbbell-shaped pleomorphic core of 140-260 nm in diameter. There are several open reading frames (ORF) along with closed hairpins on both ends of the viral genome that contains more than 180 nucleotides [6]. Several biological features of monkeypox virus are similar to variola and zoonotic orthopox viruses. These include person-to-person transmission of monkeypox virus like variola virus, however, it transmits less efficiently from one person to another as compared to that of variola virus. This person-to-person transmission is attributed to contact with the infectious oropharyngeal exudates that are produced during the rash phase of disease or during 2-3 days before the febrile prodrome period. Monkeypox virus can also infect a wide range of species of animals most commonly by causing traumatic injury to the skin. Several animal species like tree squirrels, rope squirrels, Gambian pouched rats, tree squirrels, dormice, and Gambian pouched rats have been determined to be susceptible to this virus [2].

IV. TRANSMISSION
Monkeypox virus can be transmitted via animal-to-human and also human-to-human. The animal to human transmission of the virus occurs through direct contact with bodily fluids, mucous or cutaneous lesions or blood of infected animals. The natural host of monkeypox virus has not been determined yet. However, it is thought that rodents are the most probable natural reservoir of the virus. There is evidence of presence of monkeypox virus in various animal species in Africa. These include different monkey species, rope squirrels, Gambian pouched rats, tree squirrels, dormice and others. Eating improperly cooked animal products and meat of infected animals is considered a possible risk factor for the transmission of the virus [7].

Monkeypox virus usually results from close contact with the skin lesions or respiratory secretions of an infected individual or contaminated object. Transmission of the virus through respiratory droplets is more common among household members, healthcare workers and individuals living in closed proximity due to the prolonged face to face contact among these individuals [8]. It can also be transmitted vertically from mother to fetus during pregnancy, delivery or after birth resulting in congenital monkeypox.

Recent data suggest that monkeypox virus can also be transmitted sexually from male to male as evident by the appearance of lesions around the anal or genital areas among homosexual male individuals. Several cases of monkeypox infection have been identified in communities of bisexual, gay and other homosexual men through various sexual health clinics. However, the risk of infection is not limited to homosexual men as it can also be transmitted via other means [9].

V. SIGNS AND SYMPTOMS
The early signs and symptoms of monkeypox infection include fever, headache, chills, swollen lymph nodes (lymphadenopathy), exhaustion, backaches and muscle pain. The clinical manifestations of monkeypox infection resembles that of smallpox infection except lymphadenopathy that develops early in monkeypox infection after the onset of fever. The incubation period of the virus ranges from 6-13 days but it can also vary from 5-21 days. A rash or sore appears 1 to 3 days followed by fever and lymphadenopathy. The lesions appear simultaneously and develop at a similar rate with lymphadenopathy. The lesions are usually located in peripheral areas of the body and on or around anus or genitals. In case of severe illness, these lesions appear over the whole-body including chest, face, and back areas. The number of lesions can range from a few to several thousands and can even slough off large sections of skin in severe infection. These lesions heal on their own within 4 weeks and desquamate. The rash develops into macules which evolves to papules to vesicles to pustules and finally crusts that fall off after drying. Patients with monkeypox can also suffer from a wide range of complications including respiratory distress, secondary bacterial infections, gastrointestinal involvement, sepsis, dehydration, bronchopneumonia, corneal infection and encephalitis [10].

The severity of symptoms corresponds to the patient's health status, extent of exposure to virus and underlying complications. Severe symptoms are documented most
commonly in children and individuals with immune deficiency diseases.

VI. PREVENTION

As there is no specific treatment for monkeypox infection, several measures can be adopted to prevent this infection. These include avoiding direct contact with infected animals and persons and contact with the materials previously been used by sick animals and use of personal protective equipment (PPE) around infected persons. Another important factor in preventing monkeypox infection is practicing of good hand hygiene especially washing hands with water and soap and the use of alcohol-based hand sanitizers after contact with infected humans or animals.

Monkeys can also be prevented by immunization. Immunization against smallpox infection has demonstrated 85% efficacy in preventing monkeypox infection. Individuals who were previously immunized with smallpox vaccine experienced milder illness. Recently, The US Food and Drug Administration (FDA) has approved a live, attenuated vaccine namely JYNNEOS or Imvamune or Imvamex for the prevention of monkeypox infection [11]. However, raising awareness regarding the risk factors of disease and educating people about the preventive measures are the most important factors in reducing the spread of infection.

VII. CLINICAL TREATMENT

Monkeypox infection is mostly mild and self-limiting, and the patients usually recover on their own without the need of specific therapy. These include patients with complete vaccination status of smallpox and no other illness or comorbidity. However, several patients are at high risk of developing severe disease and require proper treatment. These include individuals with diseases requiring hospitalization and other diseases like confluent lesions, encephalitis, sepsis and hemorrhagic disease, pediatric patients less than 8-years-old, breastfeeding [12] and pregnant women [13] and patients with other complications. Similarly, individuals with a compromised immune system are also at high risk of developing severe disease such as patients with AIDS, lymphoma, leukemia, solid organ transplantation, therapy with radiation, anti-metabolites, alkylating agents, high-dose corticosteroids, tumor necrosis factor inhibitors or with autoimmune disease [14].

Currently, no specific approved treatment is available for monkeypox infection. However, patients are being treated with anti-viral drugs used for treating smallpox infection. Patients need completely optimized clinical care to prevent long-term sequelae of disease, treat symptoms and manage complications. Food and Drug Administration (FDA) has approved a few anti-viral drugs that are successfully being used as medical countermeasures for treating monkeypox infection and include tecovirimat, cidofovir and vaccinia immune globulin intravenous (VIGIV). Tecovirimat has been approved for treating human smallpox disease in pediatric and adult patients and also used for treating monkeypox infection in pediatric patients having less than 13 kg body weight. Cidofovir has been approved for treating CMV (cytomegalovirus) retinitis in AIDS patients and later allowed for treatment of monkeypox and other orthopoxviruses during outbreak. Similarly, VIGIV has been used for treating the complications developed by the use of vaccinia vaccine and later approved for treating infection by orthopoxviruses during an outbreak [15].

VIII. EPIDEMIOLOGY OF MONKEYPOX IN THE UNITED STATES

The epidemiology of monkeypox in the U.S. is very rare as it does not exist naturally in the U.S. The recorded human cases of monkeypox infection in the U.S. were associated with importation of different animals from Africa in the U.S. and international human travel from areas of disease. The first monkeypox outbreak in the U.S. was reported in 2003 from six states including Wisconsin, Indiana, Ohio, Missouri, and Kansas. This outbreak comprised 47 confirmed and probable monkeypox cases. The outbreak was linked to the sale of exotic animals including prairie dogs as pets. The virus was thought to be transmitted to these susceptible non-African species during import of the consignment with African animals like rodents, that were later co-housed with individuals and contributed to the spread of infection [16].

Upon investigation, it was revealed that in April 2003, an animal shipment was imported from Ghana to Texas with almost 800 small mammals. These belonged to 9 different species with 6 types of rodents including dormice, brush-tailed porcupines, tree squirrels, rope squirrels, striped mice, and African giant pouched rats. The laboratory testing of these animals by CDC revealed monkeypox virus infection in 9 dormice, 3 rope squirrels and 2 African giant pouched rats which were housed close to prairie dogs at Illinois animal vendor facility which transmitted the virus to humans [17].

According to a study, monkeypox virus could more likely be transmitted to humans by doing specific activities with the sick animal like receiving a scratch or bite that broke the skin or touching the animal or its bedding or cleaning its cage. No human-to-human transmission of monkeypox virus was observed in the 2003 outbreak. The outbreak was contained by taking several measures like guiding the patients, veterinarians, animal handlers and healthcare providers properly, extensive laboratory testing, deployment of variola vaccine and treatment, and tracking of potentially infected individuals and animals [18].

Later, 2 cases of monkeypox were reported on July 15, and November 16, in 2021. Both the cases were associated with travel of individuals from Nigeria to the U.S. The close contacts of both the individuals were monitored for 21 days but no further cases were identified. As of May 27, 2022, a total of 12 monkeypox cases were recorded in 8 different states of the U.S. including California, Colorado, Florida, Massachusetts, New York, Utah, Virginia, and Washington. The transmission and infection source of these cases is yet to be determined. However, most cases so far have been presented via sexual health or other primary or secondary health services. Studies and efforts are underway to contain the spread of monkeypox in the U.S.
IX. EPIDEMIOLOGY OF MONKEYPOX IN THE WORLD

In 1970, the first case of human infection by monkeypox was reported in the Democratic Republic of the Congo (DRC) during the elimination period of smallpox. Several cases of monkeypox infection were also reported in several central and western African countries including Gabon, Central African Republic, Cameroon, Liberia, Cote d’Ivoire, Nigeria, Sierra Leone, and Republic of Congo. The earliest surveillance of the cases of monkeypox infection identified a total of 338 cases in DRC from 1981-86. The mortality rate of individuals in this report was 9.8% for those who were not administered smallpox (vaccinia) vaccine [19].

Another outbreak of monkeypox virus occurred in DRC in 1996-97 with a total of 511 suspected cases in 78 villages. The mortality rate was 1-5% with mild disease severity in this outbreak. Almost 78% secondary cases were observed in this outbreak that was higher than that of previous reports. Laboratory testing showed the presence of monkeypox virus in the sera of 11 suspected patients and co-infection of varicella-zoster virus among 5 monkeypox infected patients. Until now, this is the largest reported outbreak of suspected monkeypox infection cases in the zones of Lodja and Katako-Kombe in Africa [20].

In Nigeria, a total of 3 cases of monkeypox infection was recorded in 1970 and 1978 [21]. In September 2017, the largest outbreak of West African clade of monkeypox virus was reported in 26 states of Nigeria. The disease was first reported in an 11-year-old boy who presented with malaise, fever, headache, sore throat and generalized papulopustular rashes that developed into crusts and scabs. Five members of the same household developed similar clinical features. Later on, 115 confirmed and 262 suspected cases of monkeypox infection with 7 fatalities were reported from 26 states of Nigeria. It was suggested that the outbreak was the result of spill over cases from reservoir hosts of the virus [22].

Additional travel-associated cases of monkeypox infection have been reported in other countries. These include 1 case in Israel in 2018 [23] and 3 cases in UK in 2018 and 2019 [24] and 1 case in Singapore [25]. Moreover, another case was reported in UK as a result of nosocomial infection in a healthcare worker [26].

X. QUESTIONS WE CAN ANSWER ABOUT MONKEYPOX

In view of the epidemiological and clinical data regarding monkeypox infection, it can be seen that there is little data regarding the complete clinical picture of the disease and its natural reservoir. However, the previous outbreaks have shed light on the risk factors, modes of transmission and disease course after being infected. The close genetic and clinical relation between monkeypox virus and smallpox virus highlight the chances of eradication of monkeypox infection by the development of an effective vaccine similar to that of smallpox infection.

Rapid diagnosis of monkeypox infection can be done and the likely underlying viral, pathological, and immunological mechanisms can be explained in accordance with the described pathogenic mechanisms for smallpox infection. The transmission of monkeypox infection to non-African countries can be well categorized and this data can also be used to take future preventive measures and to educate community regarding additional ways to avoid contracting the infection.

XI. CONCLUSION

Monkeypox virus causes smallpox-like disease that is more fatal for young children. The re-emergence of monkeypox outbreaks in the past and present emphasizes the need of detailed scientific research on the transmission, pathogenesis, clinical treatment and therapeutic treatment regarding monkeypox infection. The recent case reports of monkeypox infection outside Africa signifies the risk of global relevance and geographical spread of infection that need to be controlled as soon as possible. Currently, proper immunization and use of PPEs near infected patients and animals are the only way to prevent infection.

REFERENCES


