International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Reemergence of Monkeypox: Prevalence, Diagnostics, and Counter Measures

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Abstract: ***Monkeypox is an emerging zoonotic disease recognized as the most important orthopoxvirus infection in humans in the smallpox post - eradication era. While monkeypox is endemic in the Democratic Republic of the Congo, it has been reported in other countries of Central and West Africa as well. The disease was also imported once into the USA. It manifests with the same symptoms as smallpox, including flu - like symptoms, fever, malaise, headache, back pain, and characteristic rash. New medications and vaccinations showed promising results for the treatment and prevention of the disease, but more studies are required to show their efficacy in the actual endemic settings. The monkeypox virus is considered a high threat pathogen causing a disease of public health importance. Therefore, there is an urgent need to focus on building surveillance capacities which will provide valuable information for designing appropriate prevention, preparedness and response activities.***

Keywords: monkey pox virus, orthopox virus, outbreak, smallpox, bioterrorism

1. Introduction

As the world is still recovering from the widespread COVID - 19 Pandemic and coming out of trauma, another outbreak known as Monkeypox Virus (MPXV) strikes. Human monkeypox is a rare viral zoonosis endemic caused by the MPXV, a member of the genus Orthopoxvirus (family Poxviridae, subfamily Chordopoxvirinae). [1] Human monkeypox is clinically almost identical to ordinary smallpox, and therefore, since the global eradication of smallpox in 1977, much attention has been paid to monkeypox as a smallpox - like disease and possible agent of bioterrorism. [1, 2] The clinical picture of monkeypox closely resembles the one of smallpox but the major difference distinguishing Monkeypox from smallpox is the lymph node enlargement that occurs early, often at the onset of fever. [3] Recently most clinical data on human monkeypox came from investigations of outbreaks in central and western Africa. It is believed that the virus is transmitted to humans during handling of infected animals or by direct contact with the infected animal's body fluids or lesions. [1] Monkeypox can infect a taxonomically wide range of mammalian species but the natural host is unknown. Monkeypox outbreaks are rarely reported, badly managed and little described leading to an incomplete picture of the disease's importance. Monkeypox is the next most pathogenic poxvirus disease after smallpox but never received appropriate attention to prevent it becoming an epidemic. [3]

This article will review the current state of knowledge about human monkeypox, with emphasis on history of the disease, epidemiology reflecting pathogenesis and clinical manifestation, diagnosis, treatment, and prevention.

1.1 History of the Disease

MPXV was identified as a member of the orthopoxvirus family in 1958 (family Poxviridae and subfamily Chordopoxvirinae) based upon the observation of lesions on infected cynomolgus macaques imported to Denmark. [4] A later blood test of animals from Africa proved that a number of African rodents had been infected with monkeypox. [5] It was not until 1970 that monkeypox was reported in humans in the Democratic Republic of the Congo. [4, 5, 6] In 1970, a nine - month - old child was admitted to the Basankusu Hospital in the Democratic Republic of the Congo, resulting in the first human MPXV case in medical history. [7] The Democratic Republic of Congo (formerly Zaire) recorded 37 documented cases of monkeypox between 1981 and 1986. [5] The first MPXV case in Nigeria was reported in 1971, and between 1971 and 1978, ten MPXV cases in Nigeria were reported. A total of several thousand human monkeypox cases have been confirmed since then, with 11 of them occurring in countries in Africa. Several countries have imported monkeypox, including the UK, the United States, Israel, and Singapore. [7] A human monkeypox outbreak particularly large in scale occurred in August 1996, and cases persisted through 1997 with peaks reported in August 1996, March 1997, and August 1997. [5, 6] Monkeypox was reported in 13 villages in Zaire between February and August of 1996, resulting in 71 clinical cases, including six deaths. [5] The number of secondary cases (person - to - person transmission) was highest in August, at the peak of the outbreak.9 of the 11 specimens collected, all were positive for monkeypox and showed only minor genetic variation compared with other strains collected during 1970 to 1979. [5, 6]

1.2 Epidemiology

Monkeypox was presumably passed in sub - Saharan Africa thousands of times, ever since humans acquired the contagion through direct contact with infected organisms. The source for MPXV is still unknown, wherein according to some research, it was predicted that the source was some kind of rodent or squirrel which were secondary inhabitants of forests of central Africa. [1] The first case of MPXV in humans was recorded in august 1970 in the rural area of DRC (democratic republic of Congo). It was a 9 - month -

old child who was admitted as a suspect of smallpox infection and his sample was sent to WHO Smallpox Reference Centre (Moscow), where it came out to be MPXV as a result of virus isolation. Also, it was stated that the baby was the only one in his family, not to be vaccinated against smallpox. [3] Ever since, there have been emerging cases of MPXV every now and then but 1981 created chaos as it registered the greatest number of cases in west Africa. DRC has also been registering the majority of MPXV cases every year. Also, few infections were recorded in Central African Republic and Sudan but it was not confirmed that the virus migrated from DRC. [8] Another outbreak was seen in 1996 - 1997 in democratic republic of Congo having an infection rate of 22 cases per 1000 population. In 2003 the virus was unstoppable and migrated outside of Africa. The first report was filed in the United state because of the shipment of rodents imported from Ghana to Texas. [9] The active MPXV surveillance program in the DRC from November 2005 till November 2007 identified 760 confirmed reports of MPXV in nine zones. There were more male than female cases. [3]

Surprisingly, no epidemiologic connection was found with Nigeria in the most recent outbreak. In may 2022 one of the US residents was reported with monkeypox after returning from Canada after that more cases have been seen from Spain, Portugal, Canada, the UK, Italy and various more. The more interesting part is they do not have any travel history to Africa. The epidemiology of MPXV has changed between different outbreaks. [10]

1.3 Pathogenesis

MPXV is a double - stranded DNA virus and the most dangerous members of the orthopoxvirus genus, the Poxviridae family, and the rest of the other member of this genus are vaccinia virus, variola virus and cowpox they all are pathogenic to human. There are two biological groups of MPXV species, the one that was found in West Africa and the other was Congo Basin. MPXV is a virus of various mammalian species including squirrels, mice, monkeys and dogs with African rodents as the source, but it periodically involves humans in regional outbreaks. [10]

The specific animal is not only the source of MPXV but also the mode of transmission of MPXV from animal to humans is unknown. It is predicted that aerosol transmission in animals may explain a nosocomial outbreak in the Central African Republic. It is also assumed that if a person comes in contact with live or dead animal or any direct or indirect contact it spreads the infection. The poor people hunt the small mammals to acquire protein rich food and this increases the exposure to wild rodents, which may carry monkeypox virus. [11] Transmission to humans occurs via blood, body fluids and inoculation from mucous membranes and skin on an infected animal. MPXV infection starts with dermis or respiratory epithelium following transmission from an infected animal or person. dispersion of the virus occurs through the lymphatics to the blood with primary viraemia and systemic infection. Secondary viraemia occurs and results in infection of the epithelium with resultant skin and mucosal lesions. Replication of the virus in mucosal surfaces can cause in its transmission via oropharyngeal secretions to close contacts. [9]

1.4 Clinical Manifestation

An average of 6 to 16 days is required for monkeypox to develop during its incubation period, which ranges from 4 to 21 days. Then comes the prodromal illness, which lasts for one to five days. Asthenia, acute myalgia, back pain, and lymph node enlargement are some of the typical symptoms of the prodromal illness. [9, 10] In the prodromal phase, also known as the pre - eruptive phase, an individual may be infectious. [9] Initially, oropharyngeal enanthem are evident, followed by papular, vesicular, pustular, and crusted lesions, eventually emerging as crusted lesions. [10] Skin rashes usually begin on the face and later spread to other parts of the body, including the palms and soles. The monkeypox is a rare cutaneous infection that can also affect the palms and soles. It is common to see facial lesions in 95% of cases. [9, 10] There are several types of skin eruptions: generalised, localised, discrete, and confluent. The lesions spread centrifugally from the face and extremities to the trunk and genitalia. [10] In contrast to the pustular phase, which lasts 5 - 7 days before transforming to scabs, each evolutional cutaneous phase takes 2 - 3 days to transform. There is a desquamation phase lasting about 1 - 2 weeks, and eruptions last for about 3 - 4 weeks. [10] People who have previously been vaccinated against smallpox have fewer and smaller lesions, less lymphadenopathy, and generally a milder form of the disease. [9] Briefly, the infection lasts 5 - 21 days, followed by a 1 - 4 day febrile stage, a 2 - 14 week rash stage, and finally a day - to - day recovery period. [10] Generally, monkeypox is a self - limiting illness lasting 14 - 21 days. The severity of the disease usually depends on the severity of the virus exposure, the health status of the child, whether they are vaccinated, the comorbidity status, and the severity of the complications. [9]

1.5 Diagnosis

The signs and symptoms of monkeypox mimic that of smallpox so somewhat similar diagnostic tests are carried on at first. The early symptoms include fever, headache, muscle ache, backache, swollen lymph nodes, tiredness, restlessness and a general feeling of discomfort. After the onset of fever for 1 - 3 days the vesicular and pustular rash develops in different parts of the body. [5] The diagnostic test for MPXV is similar to that done for any *Orthopoxvirus*. Tests such as Viral culture/isolation, Electron microscopy (staining techniques), Immunohistochemistry, PCR (Including real time PCR), etc. are proved to be very effective when studied along with proper clinical and epidemiological reports. Viral DNA is extracted and two real time PCRs are done to detect the presence of MPVX DNA. [8] Other methods are phenotypic method, it is based on the clinical diagnosis, the incubation period of MPXV is within 4 - 21 days, which ultimately follows by a prodromal illness including various signs of lymph node enlargement, myalgia, intense asthenia, pharyngitis, drenching sweats, malaise and other common symptoms and fever & headache. In electron microscopy MPXV seems to be intracytoplasmic brick shaped with lateral bodies and a central core of around 200 - 300nm. Whatsoever, this method isn't that grooming

for clinical and diagnostic areas. For the immunological method, it contains use of (ELISA) enzyme linked immunosorbent assay for IgG and IgM antibodies. It helps in distinguishing between poxvirus and herpes virus. While in genetic method or PCR, It involves PCR or RT - PCR which is advised to be done in a Biosafety level - three facility. Timely recognition of MPXV DNA and its cell culture is accomplished by this method. [7]

1.6 Treatment and Prevention

The final step in the global eradication of smallpox was the combination of vaccination and a vigorous surveillance campaign. Unfortunately, the existence of an animal reservoir makes monkeypox elimination impossible. However, vaccination with the vaccinia virus (the smallpox vaccine) is quite effective at preventing MPXV infection. In reality, research from the 1960s demonstrated that smallpox immunisation may successfully immunise monkeys against monkeypox. Pre - exposure vaccination is advised by the Centres for Disease Control (CDC) and Prevention for anyone who has direct contact with suspected MPVX - infected animals, laboratory workers who handle MPVX - possible specimens, investigators of animal or human monkeypox cases, caregivers of monkeypox patients and others. [1] The CDC advises that people who visit the ER or an outpatient clinic with a fever and vesiculopustular lesions be examined as soon as possible in a private examination room, or a negative pressure room if one is available, while keeping in mind a differential diagnosis of chickenpox, vaccinia in someone who has recently received a smallpox vaccination and even the unlikely possibility of smallpox. The modified vaccinia Ankara (MVA), a mild experimental smallpox vaccine, has been shown to be nearly as efficient as the normal smallpox vaccination at preventing monkeypox, according to a report published in March 2004 by the National Institutes of Health (NIH). [5] JYNNE STM is man - attenuated, non - replicating orthopoxvirus that is created from the modified vaccinia Ankara - Bavarian Nordic (MVA - BN strain). The US Food and Drug Administration (FDA) granted it approval in September 2019, and it is now suggested for persons 18 years of age and older who have been shown to be at high risk for contracting smallpox or monkeypox disease. Also included in ACAM2000® is live vaccinia virus. It was approved by the FDA in August 2007 and took the place of the earlier orthopoxvirus vaccine Dryvax®, which the manufacturer withdrew. For people who have been shown to have a high risk of contracting smallpox, ACAM2000® is recommended for active vaccination against the illness. [12]

The majority of people with monkeypox heal without medical intervention. There are no approved antiviral medications on the market right now to treat MPXV infection. The first antiviral approved for the treatment of smallpox in adults and children weighing at least 3kg is tecovirimat, commonly known as TPOXX or AT - 246, and is regarded as the preferred method. [12] Under the trade name Vistide, cidofovir, a broad - spectrum antiviral medication, is licensed to treat a variety of DNA viruses, including MPXV37or Gilead. [1] Since June 2021, brincidofovir has been authorised in the US for the treatment of smallpox. An oral equivalent of the injectable medication cidofovir, brincidofovir, may have a better safety profile than cidofovir, including less renal damage. FDA - approved hyperimmune globulin (VIG) is used to treat some vaccine - related side effects. [12] Because cidofovir must be provided intravenously together with probenecid and fluids to minimise renal toxicity, the risk of pharmacological therapy must be considered and evaluated against the severity of poxvirus disease. The development of modified cidofovir formulations for oral administration has showed some promise in a mouse model of orthopoxvirus infection. Other substances have demonstrated anti poxvirus action in vitro or in a variety of small animal models, but much more research must be done, particularly in nonhuman primates, before a medication with a licence to treat human monkeypox infections is available. [1]

2. Conclusion

In conclusion, monkeypox virus infection is relatively rare and usually self - limiting. With increased globalisation and cross - border movement of animals, monkeypox virus can spread to different parts of the globe. The disease, unlike smallpox, is a typical zoonosis in that most cases occur as a result of direct contact with an infected animal. The symptoms of the disease in humans can be very similar to those of smallpox, chickenpox, or other causes of vesiculopustular rash; therefore, accurate and rapid laboratory diagnostics are paramount in controlling an outbreak. Over the last decade, monkeypox has spread throughout West Africa, as well as in a number of countries across the globe. Its potential for further regional and worldwide spread continues to be a significant concern. Public health aspects of monkeypox, such as its pathogenesis, epidemiology, and clinical presentation, are still poorly understood. Smallpox vaccinations have been discontinued, which has resulted in an ecological gap where a large proportion of the population is unable to protect itself against monkeypox. In particular, we must take measures to prevent and prepare for epidemics, especially those posed by pathogens we have recognized as significant threats to human health. In order to avert new epidemics, a global effort should be made to develop better diagnostics and treatments for this viral illness.

Acknowledgement None to report

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