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Review

Monkeypox virus- Identification and significance as a preparedness to enhance public health

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ABSTRACT: Monkeypox virus is a linear double-stranded DNA virus that belongs to the family *Poxviridae* of the genus *Orthopoxvirus.* This study provides information about identification, incidence and prevalence rate and aetiopathogenesis of the monkeypox virus in Africa and also the study of its epidemiology on human is well explained. However, the study gives details about the clinical manifestation, laboratory testing, mode of transmission and preventive way to cure and reduce the virus. Nevertheless, the Centre for Disease Control (CDC) and Prevention recommends the use of smallpox vaccine within two (2) weeks of significant exposure and antiviral agents like Cidofovir have also been employed. Improved infection control measures include: regular screening and isolation of newly infected animal, better hygiene habits, and quarantining of infected persons. A better understanding of monkeypox virus would contribute to better management of emergency situations.

Keywords: Epidemiology, incidence, *Orthopoxvirus,* prevalence, smallpox.

INTRODUCTION

Monkeypox is a rare disease that is caused by infection with monkeypox virus. Monkeypox virus belongs to the *Orthopoxvirus* genus in the family *Poxviridae*. The *Orthopoxvirus* genus also includes Variolavirus (the cause of smallpox), Vaccinia virus (used in the smallpox vaccine), and Cowpox virus. It is an enveloped slightly pleomorphic; dumbbell-shaped core with lateral bodies; 140 to 260 nm in diameter by 220 to 450 nm in length (Figure 1) (Reynolds and Damon, 2012).

Monkeypox was first discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of crab-eating monkeys, *Macaca cynomolgus* kept for research in a laboratory at Serum State Institute, Copenhagen, hence the name 'monkeypox'. The first human case of monkeypox was recorded in 1970 in the Democratic Republic of Congo (DRC) during a period of intensified effort to eliminate smallpox. Since then monkeypox has been reported in humans in other central and western African countries (Joanne et al., 2008).

The 2003 outbreak in the United States is the only time monkeypox infections in humans were documented outside of Africa (CDC, 2003). The natural reservoir of monkeypox remains unknown. However, African rodent species are expected to play a role in transmission. There are two distinct genetic groups (clades) of monkeypox virus—Central African and West African. West African monkeypox is associated with milder disease, fewer deaths, and limited human-to-human transmission (Reynolds and Damon, 2012).

Public health is a branch of medical sciences that primarily deals with the surveillance, control, detection and prevention of the emergence and spread of infectious diseases in a defined human population. It involves the protection and improvement of the health of the general public. In clinical medicine, doctors and nurses practice their profession by looking at the health issues of individuals who turn out to be their patients, but in the practice of public health, the entire community and not individuals are regarded as patients (Nasir et al., 2018). Public health is a field of the medical sciences that ensures

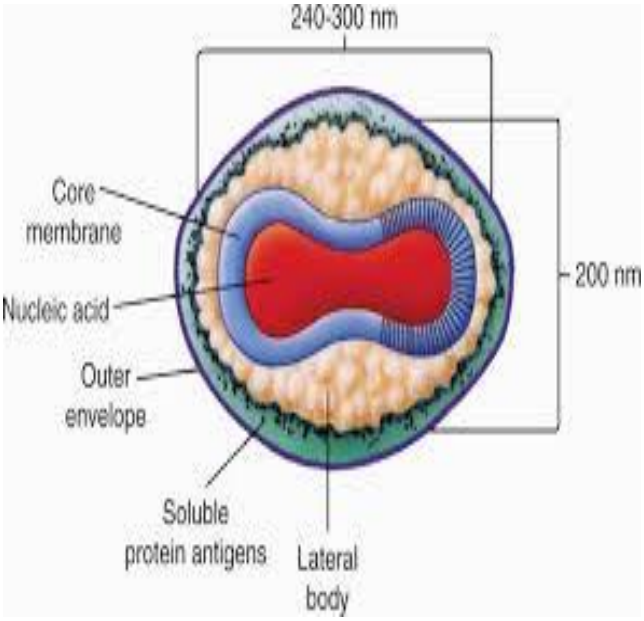

Figure 1. Structure of a Poxvirus. (Prescott et al., 2008).

improved quality of life for the general public by making sure that people imbibe good environmental sanitation and personal hygiene aside other relevant precautionary measures as sustainable means of restraining the emergence and spread of infectious diseases (Nasir et al., 2018).

Public health professionals go beyond treating individuals when they fall sick or become injured (which is usually the main task of clinicians) to preventing infectious diseases and other health-related emergency from either occurring or re-occurring within a specific human population. It is the scientific discipline that promotes the health of the general public by preventing, detecting and controlling infectious diseases as they emerge.

Infectious diseases are a leading cause of morbidity and mortality across the globe, and they have more ravaging effects in developing or low income countries where environmental sanitation, water supply, standard of living, medical care amongst other developmental factors are still poor. Infectious diseases including monkeypox, malaria, HIV/AIDS, cholera, Ebola virus, Lassa fever, multidrug resistant bacteria, hepatitis, gonorrhea, influenza, tuberculosis and food borne diseases impose colossal economic burden on the entire society. They can cripple the workforce of any nation if taken lightly, and thus timely detection and containment is paramount amongst all other factors. A well trained, prepared and proactive public health labor force is critical in any nation as a panacea to dealing with the threats of emerging and re-emerging infectious diseases (Li et al., 2017).

Due to the emergence of monkeypox virus in the world and low level of its awareness, this study therefore, reviews monkeypox virus as a significance to enhance public health.

EPIDEMIOLOGY

Monkeypox is considered endemic in the Northern and Central Democratic Republic of Congo. People living in or near the forested areas may have indirect or low-level exposure, possibly leading to subclinical infection. The disease is rare and only known to be indigenous to the rain forests of western and central Africa. It was first recognized in humans in 1970 after the eradication of smallpox, possibly because of the subsequent unmasking of the infection. Surveillance reports from 1981 to 1986 documented 338 cases in the DRC (out of a 1982 estimated population of 5 million). In the 1996 to 1997 outbreaks in the DRC, the attack rate was 22 cases per 1000 population (Hutin et al., 2001).

Human infection with monkey pox has not been reported in West Africa since 1978. However, monkeypox continues to exhibit a robust emergence in the Democratic Republic of Congo (DRC), with sporadic occurrences of disease in neighboring countries. In 2003, 11 cases and 1 death were reported from the DRC (CDC, 2003) and 10 cases with no deaths were reported from Sudan in 2005. In United States, no cases occurred until the late spring 2003 outbreak in the Midwestern states. Between May 16 and June 20, 2003, 71 suspected cases of monkeypox were investigated (Reynolds and Damon, 2012).

In 2017, Nigeria recorded a total of 172 cases (with 61 confirmed cases) of monkeypox in 22 states; AkwaIbom, Bayelsa, Cross River, Delta, Ekiti, Enugu, Imo, Lagos, Abuja and others African cases have mortality rates of 1 to 10%with the highest rate occurring in children (Mahendra et al., 2017).

AETIOPATHOGENESIS

In Africa, outbreaks of monkeypox in humans are primarily associated with hunting, skinning, preparing and eating of infected rodents and monkeys. It should be noted that the natural host for monkeypox virus are rodents. Viral entry from a wildlife source probably occurs via small lesions on the skin or oral mucous membranes. The Incubation period for Monkeypox ranges from 10 to 14 days (on average 12 days) before the virus start replicating itself (Mahendra et al., 2017). Monkeypox virus replicates in lymphoid tissues, it causes lymphadenopathy. The virus first localizes in mononuclear phagocytic cells, is released into the bloodstream, and then localizes again in skin cells (Mahendra et al., 2017).

INCIDENCE AND PREVALENCE

It was first recognized in humans in 1970 after the eradication of smallpox, possibly due to the subsequent unmasking of the infection. Surveillance reports from 1981 to 1986 documented 338 cases in the DRC (out of a 1982 estimated population of 5 million). In the 1996 to 1997

outbreaks in the DRC, the attack rate was 22 cases/1000 populations. Monkeypox is endemic in highly forested regions of DRC. Sporadic occurrences of disease are reported in neighboring countries. In 2003, 11 cases and 1 death were reported from the DRC and 10 cases with no deaths were reported from Sudan in 2005. Human case of Monkeypox was reported in Sierra Leone in 2014 and 2017 (Nasir et al., 2018).

Initial epidemiological studies conducted during 1970 to 1979 detected a total of 47 cases of human Monkeypox virus near rainforests of sub-Saharan Africa, of which 38 occurred in the DRC and the remainder in Cameroon, the Central African Republic, Gabon, Cote d'Ivoire, Liberia, Nigeria and Sierra Leone. All cases in the DRC occurred in areas bordering tropical rainforests and appeared to be associated with animal contact. Seven of the 47 reported infections were fatal. The secondary transmission was determined to be the most likely cause of infection in four cases, with secondary attack rates of 7.5% among close family members living in the same household and 3.3% among all susceptible contacts. Since 1980, the vast majority of cases have continued to be reported from the DRC (Nasir et al., 2018).

During 1986 to 1992, only 13 cases were reported in the literature, and none were reported during 1993 to 1995. However, in 1996 to 1997, more than 500 suspected cases of Monkeypox virus were reported in Kasai-Oriental province, DRC. Only a small number of these cases were laboratory confirmed, and in contrast to the findings of the earlier World Health Organisation (WHO) study, the percentage of secondary cases was much higher (78%) and the fatality rate much lower (1 to 5%), suggesting that the great majority were actually cases of varicella. No reports of new suspected Monkeypox virus cases were published until 2001, when 31 patients with Monkeypox virus in seven separate disease clusters were described in Equateur province, DRC.

Between 1 January 1998 and 31 December 2002, a total of 1265 cases were reported to the DRC Ministry of Health, with specimens collected in 215 cases. Of these 215 cases, PCR and virus culture revealed that 88 were due to Monkeypox virus. An active disease surveillance system is currently being established in Kasai-Oriental province, DRC, which promises to provide more-extensive and reliable data on the disease.

An outbreak of Monkeypox virus occurred in the Midwestern United States in 2003 (Nasir *e*t al., 2018). There were total of 47 confirmed and probable cases in six states, 18 of whom were hospitalized. Half of the cases were confirmed by laboratory testing. There were no deaths from this West African strain of Monkeypox virus, which as described causes a milder illness in humans than does of the Central African strain.

On 27th October 2017, the Federal Government of Nigeria confirmed six cases of Monkeypox virus. The cases are amongst those sent to the World Health Organization's laboratory in Dakar, Senegal, a statement by the Ministry of Health. The Nigerian Minister of State for Health said two cases each were confirmed in Bayelsa and Akwa Ibom States, one each in Enugu State and the Abuja. They bring to nine the total number of MKPX cases so far confirmed in Nigeria. Three MKPX patients had earlier been confirmed on October 16, 2017. Meanwhile, there are 94 suspected cases reported from 11 states, namely, Akwa Ibom, Bayelsa, Cross River, Delta, Ekiti, Enugu, Imo, Lagos, Nasarawa, Niger, Rivers and the Federal Capital Territory.

A total of 228 suspected MKPX cases were reported from 24 States and the FCT as at 25th February, 2018. Out of this, 89 cases have been confirmed in 15 States. (Nasir et al., 2018). A total of six deaths have been recorded since the outbreak, four of which are in patients with background immunosuppressant. Clustering of cases was revealed in Bayelsa, Rivers and Imo States but no evidence of epidemiological linkages across States was revealed.

MODE OF TRANSMISSION

Monkeypox virus can be transmitted through (Mahendra et al., 2017);

1. Direct contact with infected animals including a bite from animals, as well as contact with animal blood, body fluid, or rash.
2. Person-to-person transmission also occurs, primarily through large respiratory droplets spread during periods of long face-to-face contact (This is usually during the first week of rash).

CLINICAL FEATURES

Nonhuman primates

In nonhuman primates, the predominant syndrome is a self–limiting rash. The initial clinical signs include fever and 1-4 mm cutaneous papules, which develop into pustules, then crust over (Plate 1). A typical monkeypox lesion has a red, necrotic, depressed center, surrounded by epidermal hyperplasia. These "pocks" can be seen over the entire body, but may be more common on the face, limbs, palms, soles and tail. The number of lesions varies from a few individual pocks to extensive, coalescing lesions (Daniel et al., 2016). The crusts over the pustules eventually drop off, leaving small scars. Some animals have only skin lesions. In more severe cases, there may also be respiratory signs (coughing, nasal discharge, dyspnea), anorexia, facial edema, oral ulcers or lymphadenopathy. Disseminated disease with visceral lesions is uncommon in natural infections among nonhuman primates. Pneumonia is common only in monkeys infected experimentally via aerosols. Most

Plate 1. Manifestation of Monkeypox in monkeys (Morand et al., 2017).

naturally infected animals recover; however, fatalities are sometimes seen, particularly in infant monkeys. Asymptomatic infections also occur (Mahendra et al.,2017; Morand et al., 2017).

Prairie dogs

In prairie dogs, the clinical signs may include fever, depression, anorexia, weight loss, nasal discharge, sneezing and/or coughing, respiratory distress, diarrhea, a nodular skin rash and oral ulcers. During the outbreak in the U.S., blepharoconjunctivitis was often the first sign. Lymphadenopathy has been reported in naturally infected prairie dogs, but did not occur in all experimentally infected animals. Elevated serum levels of liver enzymes have also been seen. In experimentally infected prairie dogs, skin lesions appeared first on the head or extremities, followed by the trunk. On the trunk and limbs, characteristic monkeypox lesions developed from macules through vesicles and pustules before forming scabs. Macules and vesicles also occurred on the face in this experiment, but pustules were not seen. Infected prairie dogs may either recover or become fatally ill. Some experimentally infected prairie dogs died 1 to 2 weeks after infection without developing lesions on the skin or mucous membranes (Zaucha et al., 2001).

Other rodents

Little is known about the effects of monkeypox virus on most rodent species. In dormice inoculated intranasally, the clinical signs were limited to lethargy, an unkempt hair coat, a hunched posture, conjunctivitis and dehydration. Many infections were fatal. Experimentally infected cotton rats developed an acute illness with rhinitis, conjunctivitis, dyspnea, coughing and progressive emaciation, often ending in death. In ground squirrels, the first signs were anorexia and lethargy. Nasal hemorrhages and dyspnea were common with a Congo Basin isolate, but most ground squirrels inoculated with a West African strain did not have nasal hemorrhages, and respiratory distress occurred only terminally. Both strains were uniformly fatal at the dose used (Mahendra et al., 2017; Maksyutov et al., 2016).

Fatal infections were reported among rope squirrels and one Gambian giant pouched rat in the shipment of exotic African rodents to the U.S. Mild clinical signs, with no respiratory signs and limited skin lesions, were seen in another Gambian giant pouched rat in the shipment. Some pouched rats that appeared healthy were seropositive (Stern et al., 2016).

At necropsy, the skin may contain papules, umbilicated pustules (“pocks”) with central necrosis, or crusts over healing lesions. The skin lesions may vary from barely detectable, single small papules to extensive lesions. Ulcers, erosions or lesions with necrotic centers may be found in the mouths of some animals. Lesions (e.g., white plaques, or small, white, firm, deeply embedded foci with umbilicated necrotic centers) have sometimes been found on internal organs. Additional visceral lesions including (but not limited to) multifocal necrotizing pneumonitis, orchitis and peripheral lymphadenopathy may be seen. Blepharoconjunctivitis is a common finding in prairie dogs (Zaucha et al., 2001).

In intranasally inoculated dormice, the gross lesions at necropsy included hepatomegaly, lymphadenopathy and hemorrhages in the upper gastrointestinal tract, nasal cavity, gall bladder and brain. Pulmonary edema and hemorrhages were reported in experimentally infected ground squirrels (Prescott et al., 2007).

In humans

In humans, monkeypox resembles smallpox; however, the symptoms are generally milder, and unlike smallpox, the lymph nodes are usually enlarged. The initial symptoms are flu–like and may include malaise, fever, chills, headache, sore throat, myalgia, backache, fatigue and a nonproductive cough. Lymphadenopathy most often affects the submandibular, postauricular, cervical and/or inguinal lymph nodes. Nausea, vomiting and conjunctivitis

Plate 2. Manifestation of monkeypox virus in humans (Morand et al., 2017).

were reported from some cases in the United State (Joanne et al., 2008). A rash, initially characterized by macules and papules, develops one to several days after the prodromal signs; these lesions develop into vesicles and pustules (“pocks”), which umbilicate, form scabs and are eventually shed. The number of skin lesions varies from less than 25 to more than a hundred (Plate 2). They are usually concentrated on the extremities, but can also be seen on the head and torso. Lesions may develop on the mucous membranes, as well as on the palms, soles and genitalia. Confluent rashes and recurrent febrile periods can occur in severe cases. Corneal ulceration, coagulation disorders, respiratory complications including dyspnea, encephalitis (rarely) and multiorgan failure have also been reported. Although most patients survive, some cases end in death. In patients who recover, the illness generally lasts for 2 to 4 weeks, and the skin lesions usually resolve within 14 to 21 days. Residual varioliform scarring, with hypopigmented and/or hyperpigmented skin lesions, may be a sequela. Severe scarring, as seen in smallpox, is rare. Subclinical and very mild cases have also been reported (Iizuka et al.,2017).

LABORATORY INVESTIGATIONS

In animals

The characteristic skin lesions are suggestive of monkeypox, and histopathology provides supportive evidence. The diagnosis can be confirmed by virus isolation or Polymerase Chain Reaction (PCR) assay. Monkeypox virus can be recovered in mammalian cell cultures, and may be identified using PCR followed by Restriction Fragment– Length Polymorphism (RFLP) analysis or sequencing (Meyer *et al.,* 1997). Monkeypox-specific PCR assays are available in some laboratories, and a DNA oligonucleotide microarray can identify this virus rapidly and specifically. PCR can also be performed directly on clinical samples (Maksyutov et al., 2016).

If the animal has not been exposed to other orthopoxviruses, monkeypox can be tentatively diagnosed by detecting orthopoxvirusvirions with electron microscopy or orthopoxvirus antigens by immunohistochemistry. However, the specific virus cannot be identified with these techniques (Guarner et al., 2002).

Samples of skin lesions and conjunctival swabs may be collected from live animals. Monkeypox virus has also been detected in blood, and sometimes in oral and nasal secretions (e.g., oropharyngeal swabs), urine and feces. At necropsy, tissues should be collected from all organs that have lesions. In prairie dogs, monkeypox viruses, viral DNA or antigens have been detected in skin lesions, eyelid and tongue samples, and in many internal organs including the lung, liver, spleen and lymph nodes. In dormice, monkeypox viruses have been found in most organs and tissues. One study suggested that the liver contained particularly large amounts of virus in this species (Li et al., 2017).

In humans

Monkeypox can be tentatively diagnosed if the characteristic skin lesions are present and there is a history of exposure. Tests to isolate the virus, or identify its nucleic acids or antigens, are similar to those used in animals. In humans, monkeypox virus can be found in skin

lesions (e.g., in scabs or material from vesicles) or throat and nasopharyngeal swabs. Serology may also be helpful. Convalescent-phase serum can be tested for orthopoxvirus-specific IgM with an Enzyme-Linked Immunosorbent Assay (ELISA) if the lesions have resolved. Cross-reactions between orthopoxviruses, including smallpox and monkeypox viruses, can occur in serological tests (Guarner et al.,2002). The possibility of exposure to undiscovered orthopoxviruses also complicates the interpretation of serology in endemic areas. Cross-adsorbed virus neutralization, immunofluorescence or hemagglutination inhibition assays, as well as immunoblotting (Western blotting), can be used to distinguish reactions between monkeypox virus and smallpox virus, although some of these assays are not always easy to interpret. A specific ELISA that may detect monkeypox antibodies in people vaccinated for smallpox has been reported in the literature (Mahendra et al.,2017).

DISEASE MANAGEMENT

There is no known definitive treatment. However, the Center for Disease Control (CDC) and Prevention recommends smallpox vaccine within two (2) weeks, ideally before four (4) days after a significant, unprotected exposure to an infected animal or a confirmed human case. Data from African outbreaks suggest that prior smallpox vaccination confers 85% protection from monkeypox viral infection (CDC, 2003).

Antiviral agents like Cidofovir have also been used. However, antiviral chemotherapeutic treatment is not a viable option in remotes places where the disease is likely to appear. In addition, the treatment is not devoid of side effects (Stern et al., 2016).

BIOTERRORISM

Monkeypox cannot be weaponized but it might be used to create widespread panic in a population as it has almost similar presentation to smallpox and since creating panic is a form of terrorism, the use of monkeypox as a bioweapon cannot be completely ruled out (Guarner et al., 2003).

PREVENTION

There are number of measures that can be taken to prevent infection with monkeypox virus and they include (Mahendra et al., 2017):

1. Avoid contact with animals that could harbor the virus (including animals that are sick or that have been found dead in areas where monkeypox occurs.
2. Avoid contact with any materials, such as bedding, that has been in contact with a sick animal.
3. Isolate infected patients from others who could be at risk for infection.
4. Practice good hand hygiene after contact with infected animals or humans. For example, washing your hands with soap and water or using an alcohol-based hand sanitizer.
5. Use Personal Protective Equipment (PPE) when caring for patients.

CONTROL

Improved infection control measures including the regular screening and isolation of newly infected animals. This is to prevent outbreaks among other animals. During an outbreak of monkeypox, viral spread maybe controlled by quarantining (at least for 6 weeks from the date of last exposure) the infected animal or human and tracing their contacts. Areas where these animals have been kept should be cleaned and disinfected thoroughly (Reynolds et al., 2010).

CONCLUSION

It has been observed that the newer pox viruses could be like the eradicated smallpox virus which causes a potentially life threatening infection in humans. Therefore, a better understanding of monkeypox virus and similar microorganisms could contribute to better management of emergency situations and aid public health.

CONFLICT OF INTEREST

The authors declare that there was no conflict of interest.

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