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Epidemiology, Diagnosis, and Control of Monkeypox Disease: A comprehensive Review

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Abstract Human monkeypox is an emerging viral zoonotic disease, which is caused by monkey pox virus. The disease occurs mostly in the rain forests of central and western Africa. People living in or near the forested areas may have indirect or low-level exposure, possibly leading to subclinical infection. However, the disease recently emerged in the United States in imported wild rodents from Africa. Monkeypox has a clinical presentation like ordinary forms of smallpox, including flulike symptoms, fever, malaise, back pain, headache, and characteristic rash. In view of the eradication of smallpox, such symptoms in a monkepox endemic region should be carefully diagnosed. Primarily, monkey pox transmission to humans is believed to occur through direct contact with infected animals or possibly by ingestion of inadequately cooked flesh. Infection by inoculation through contact with cutaneous or mucosal lesions on the animal, especially when the skin barrier is compromised secondary to bites, scratches, or other trauma is a possibility. Laboratory diagnosis is imperative because it is clinically indistinguishable from other pox-like illnesses. There are no licensed therapies to treat human monkey pox viral infection; however, the smallpox vaccine can protect against the disease. The discontinuation of general vaccination in the 1980s has given rise to increasing susceptibility to monkey pox virus infection in the human population. This has led to fears that monkey pox virus could be used as a bioterrorism agent. Effective prevention relies on limiting the contact with infected patients or animals and limiting the respiratory exposure to infected patients.

Keywords: *monkeypox, public health, virus, zoonosis*

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1. Introduction

Monkeypox is a smallpox-like viral infection caused by a virus of zoonotic origin, which belongs to the genus *Orthopoxvirus*, family *Poxviridae*, and sub-family *Chordopoxvirinae*. It was first isolated in 1958 from a group of sick monkeys (*Macaca cynomolgus*). Human infection with Monkeypox virus was first described in central Africa in 1970 in a 9-month old child from Zaire [1,2,3]. The disease is endemic in the Congo basin countries of Africa and, possibly, West Africa as well with majority of human cases being reported from countries in the Congo basin [4,5,6].

Smallpox is a serious, contagious, and sometimes fatal infectious disease and the name is derived from the Latin word for "spotted" and refers to the raised bumps that appear on the skin of face and body of an infected person. Smallpox outbreaks have occurred from time to time for thousands of years, but the disease is now eradicated after a successful worldwide vaccination program. The last naturally occurring case in the world was in Somalia in 1977. After the disease was eliminated from the world, routine vaccination against smallpox among the public was stopped because it was no longer necessary for prevention. In 1970, when smallpox was nearly eradicated, a previously unrecognized orthopoxvirus named monkey pox was identified in humans. The first known human case occurred in the Equateur province of Zaire (now known as the Democratic Republic of Congo (DRC) when a 9-year-old boy developed smallpox like illness, which was eventually confirmed as human monkey pox by the World Health Organization [4]. Retrospectively, similar cases occurring in 1970-1971 from the Ivory Coast, Liberia, Nigeria, and Sierra Leone were attributed to monkeypox infection.

Monkeypox virus was discovered in 1958, when it was isolated from the lesions of a generalized vesiculo-pustular disease among captive monkeys at the State Serum Institute, Copenhagen [7]. The close resemblance between smallpox and monkeypox in captive primates focused attention on monkey pox virus as a potential threat to smallpox eradication.

Prior to 1970, monkey pox, a disease caused by the *Orthopoxvirus*, monkeypox virus *(*MPXV), was recognized only in non-human hosts. Between 1970 and 1986, 10 cases of human monkey pox were reported from Western African countries (Sierra Leone, Nigeria, Liberia and Côte d'Ivoire) and 394 cases were reported from the

Congo Basin countries of Cameroon, Central African Republic and Zaire (now Democratic Republic of the Congo) [8].

Monkeypox was limited to the rain forests of central and western Africa until 2003, when the first cases in the Western Hemisphere were reported. In late spring 2003, multiple persons were identified in the Midwestern United States who had developed fever, rash, respiratory symptoms, and lymphadenopathy following exposure to ill pet prairie dogs (a rodent of *Cynomys* species) infected with the monkeypox virus [9].

A direct contact or exposure with ill, prairie dogs (a group of herbivorous burrowing rodents), showing signs of profuse nasal and ocular discharge, dyspnoea, lymphadenopathy, and muco-cutaneous lesions was noted among the cases reported. Another interesting observation noted among those cases was the presence of a common animal distributor where prairie dogs were housed or transported along with African rodents from Ghana. Reports have later confirmed that most cases of monkeypox were associated with exposure to these rodents, the local Gambian rats, which were known reservoirs of monkeypox in their native habitat of Africa. After an exposure, and an average incubation period of 12 days, the animal became ill and has a potential to transmit the virus to humans, when present in close proximity. Human-to-human, disease transmission leading to an outbreak was reported from DRC during 1996-1997 [6]. Studies reported from this outbreak suggested that within households, monkeypox virus was secondarily transmitted to 8-15% of human contacts. Prior to this, monkey pox was not identified as an important worldwide health problem because human infection rates were either not known or were undermined to play a significant role in the pathogenesis. Analysis of the 2003 US outbreak implicates animal-to-animal and animal-to-human transmission as the significant modes of transmission.

Genomic sequencing of monkeypox strains isolated from the America, western and central Africa's, has noted the existence of two distinct clades of the virus. The isolates from the United States were found to be identical with the western African strains. The clinical course of the disease among people infected with the western African strain was observed to be milder with minimum human-to-human transmission as compared to those infected with isolates from central African region [10]. In 2010, a dosage comparison using a prairie dog animal model
re-confirmed that the Congo Basin strain of monkeypox virus was more virulent than the West African strain of monkeypox virus [11]. This communication presents a comprehensive review on the epidemiology, diagnosis and control of monkeyox, an emerging viral zoonosis, which attracted the attention of public health authorities.

2. Classification and Characterization of Monkeypox Virus

The monkeypox virus belongs to *Poxviridae* family, which also includes cowpox, vaccinia, and variola (smallpox) viruses. Poxviruses are the largest vertebrate viruses known, infecting humans, and other vertebrates (species of sub-family *Chondropoxvirinae*), and arthropods (species of sub-family *Entemopoxvirinae*). There are around 70 known species of pox viruses spread among 28 genera and two sub-families (the *Chordopoxvirinae* and the *Entomopoxvirinae*). The virions contain a linear double-stranded deoxyribonucleic acid (dsDNA) genome and enzymes that synthesize messenger ribonucleic acid (mRNA). They multiply in the cytoplasm of the host cells.

The *Chordopoxvirinae* consists of around ten genera including the genera which are genetically and antigenetically related. The genus Orthopoxvirus comprises camelpox, cowpox, ectromelia, monkeypox, racoonpox, skunkpox, taterapox, Uasin Gishu (pox virus of Horse), vaccinia, variola and volepox. African swine fever viruses were also known to share some properties of the poxviruses. Many poxviruses are associated with a specific vertebrate species, which indicates that the transmission of these viruses occurs preferentially among a specific vertebrate species. Although accidental transmission in to a different vertebrate species can occur, there was no resultant clinico- pathological condition noted in the infected host to be further maintained in this 'aberrant' species [12]. The orthopoxviruses which can infect humans include variola, vaccinia, cowpox and monkeypox viruses. Variola virus is a virus which only infects humans and the Vaccinia virus is a vaccine strain that does not exist in nature and is used to treat small pox. Vaccinia virus has originated in the 18th Century from an unknown vertebrate species. Cowpox is a rodent virus that may infect cats, cows and zoo animals and could transmit infection to humans.

Monkeypox is also a rodent virus, which occurs mostly in West and Central Africa. The identification of monkeypox virus is based on biological characteristics and endonuclease patterns of viral DNA. In contrast to smallpox, monkeypox virus can infect rabbit skin and can be transmitted serially by intracerebral inoculation of mice. The four orthopoxviruses that may infect man produce macroscopically characteristic lesions on the inoculated chorioallantoic membrane of an embryonated chicken egg [8]. The maximum or 'ceiling' temperature at which the viruses can proliferate in the chorioallantoic membrane differs for monkeypox and smallpox. These viruses differ also in the ability to multiply in different tissue culture cells. However, at present the clearest results are obtained by the endonuclease restriction patterns of the virus DNA [13]. Some genetic variability has been noted between monkeypox viruses isolated from West and Central African regions. Genome studies have revealed strong evidence regarding monkeypox virus being a non-ancestral to variola virus. This may be important in view of the fear expressed by some researchers that variola might again evolve from monkeypox virus. In the pre-molecular era, significant efforts were made to distinguish the four viruses by serological reactions. These were delicate studies, since the viruses share most antigens [14]. Some results were obtained using absorbed sera in agar gel diffusion tests, but they were rapidly superseded by the studies on biological characteristics and DNA restriction patterns. The development of relatively specific antigens has been extremely useful for serological surveys in human and animals. In the field, rapid presumptive

diagnosis of infection caused by viruses belonging to the *orthopoxvirus* group is necessary, as is differentiation from chickenpox, as confusion is possible on clinical grounds. For this purpose, it is recommended that scabs of the lesions are sent, without transport medium, to the diagnostic laboratory. Electron microscopic examination of this material will allow the differentiation of *Orthopox* and *Herpes* viruses. Poxviruses can be detected in more than 95% of the scabs, whereas varicella-zoster virus could be detected in only half of the material from cases of chickenpox, meaning that electron microscopy negative specimens are very unlikely to be monkeypox [8,15,16].

3. Epidemiology

3.1. Occurrence

People living in or near the forested areas may have indirect or low-level exposure, possibly leading to subclinical infection [17]. 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 1981-1986 documented 338 cases in the DRC (out of a 1982 estimated population of 5 million). In the 1996-1997 outbreaks in the DRC, the attack rate was 22 cases per 1000 population. Human infection with monkey pox has not been reported in West Africa since 1978. However, monkeypox continues to exhibit a robust emergence in the DRC, with sporadic occurrences of disease 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 [18]. 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 [19].

3.2. Mortality/Morbidity

Rash burden, hospitalization rates and illness severity (a global score incorporating degree of incapacitation, need for nursing care and rash burden) were used to define human disease

Morbidity during a monkeypox infection. Monkeypox case-fatality rates in Democratic Republic of the Congo were ~10% among non-vaccinated individuals as compared to those people who were vaccinated against smallpox, and the vaccinated group was noted to have fewer lesions and generally less severe disease [8].

The disease was generally self-limited, with resolution in 2-4 weeks, depending on the severity of the illness. However, a small subset of patients, most commonly pediatric patients, had a more severe course, with several patients requiring ICU care [20]. Complications reported from African outbreaks include pitted scars, deforming scars, secondary bacterial infection, bronchopneumonia, respiratory distress, keratitis, corneal ulceration, blindness, septicemia, and encephalitis.

African cases have mortality rates of 1-10%, with the highest rates occurring in children and individuals without vaccination. In general, the prognosis is related to the amount of exposure to the virus, host immune response, comorbidities, vaccination status, and severity of complications. Poxvirus infections have no racial predilection and the incidence is equal in males and females.

In the African epidemics, 90% of the patients were children younger than 15 years [21]. In the recent US outbreak, of the confirmed cases in 2003 (n = 35), 11 patients were younger than 18 years and 24 were older. Although the highest age-specific incidences and the greatest number of cases occur among persons younger than 15 years, a trend toward increasing incidence among persons aged 15-30 years has been seen in recent years. It has been hypothesized that cessation of smallpox vaccination may be a factor in the increasing incidence in this age group, but this theory fails to account for why the disease has not re- emerged in countries where the disease was seen previously, such as West Africa [18]. An annual crude incidence rate of human monkey pox of 0.63/10,000 population was inferred. Those at high risk were young unvaccinated children (especially boys) and adult women. Approximately one third of the infections were estimated to be sub-clinical [22]. The increase in cases was ascribed to the effect of the civil war which had led to increased hunting for forest animals that carry monkey pox, particularly squirrels. With changes in lifestyle due to increasing urbanization, and intensified agricultural activities replacing hunting and trapping, the chances of contracting monkey pox, either from the primary reservoir or intermediate hosts, will decrease and monkey pox will become a disappearing disease.

3.3. Transmission

It is a zoonotic virus with primary transmission believed to occur through direct contact with infected animals or possibly by ingestion of their inadequately cooked flesh. Inoculation may be from cutaneous or mucosal lesions on the animal, especially when the skin barrier is compromised secondary to bites, scratches, or trauma. Transmission can also occur from animal reservoirs from Western Africa (prairie dogs, rabbits, rats, mice, squirrels, dormice, monkeys, porcupines, gazelles). Additionally, direct cutaneous (skin-to-skin) or respiratory contact with an animal or person who is infected can transmit the infection.

3.4. Hosts and Reservoirs

Although rodents are believed to be the major reservoir in Africa, A 2010 study reaffirmed that several species of forest-dwelling rodents are at risk of developing Orthopoxvirus (including monkey pox) infection [23,24].

Serological surveys suggest that many animals are infected with MPV under natural conditions, including squirrels, non-human primates, and rats. Several epidemiological studies from the Democratic Republic of Congo have implicated squirrels (especially *Funisciurus anerythrus*) inhabiting agricultural areas as primary candidates to sustain viral transmission among people in nearby settlements [24]. In one environmental survey, *Funisciurus* spp. squirrels had a higher rate of MPV

seropositivity (24%) than other animals that were tested, including *Heliosciurus* spp. squirrels (15%) and primates (8%). A subsequent seroprevalence study done as part of the investigation of the outbreak in February 1997, in the Democratic Republic of Congo showed even higher positivity rates in these squirrels (39—50% in *Funisciurus* spp. and 50% in *Heliosciurus* spp. squirrels) [6]. In addition, 16% of Gambian giant rats tested in this study had serological evidence of MPV exposure. The infection of a rabbit (family *Leporidae*) after exposure to a diseased prairie dog at a veterinary clinic confirmed the transmissibility of the virus between mammal species common in North America. Little is known about coinfection with MPV and HIV [25].

4. Clinical Presentation

The clinical presentation of human monkeypox was described primarily among children and adolescents identified in central and West African regions. The disease was characterized as a viral prodrome fever with chills, headache, myalgias, and back pain lasting for 1–3 days, followed by a maculopapular exanthematous eruption. The rash was predominantly monomorphic with a centrifugal distribution, progressing to vesicular, pustular, and finally developing crusts during a 2– 3-week period [21,26].

Monkeypox viral infection can cause a syndrome clinically like smallpox but was noted to be less infectious and clinically milder. The incubation period averages 12 days, ranging from 4-20 days. In the prodrome or pre-eruptive stage (lasts 1-10 days), fever could be the first symptom (usually 38.5-40.5°C). The febrile illness may often be accompanied by chills, drenching sweats, severe headache, backache, myalgia, malaise, anorexia, prostration, pharyngitis, shortness of breath, and cough (with or without sputum). Lymphadenopathy might appear within 2-3 days after the fever in most cases. In the 2003 outbreak, 47% of patients had cervical lymphadenopathy, with nodes measuring several centimeters in diameter. In the exanthematous stage, most infected people develop a rash within 1-10 days after the onset of fever. The rash often starts on the face and then spreads to the rest of the body, and could persist for 2-4 weeks until all lesions have turned to crusts. Encephalitis with immunoglobulin M (IgM) was observed in the cerebrospinal fluid as reported in a previous research [27].

In the exanthematous stage, within a body region, lesions evolve synchronously over 14-21 days, like the development of lesions with smallpox. However, unlike smallpox, skin lesions may appear in crops. In contrast to smallpox, the lesions do not have a strong centrifugal distribution. Lesions progress from macules to papules to vesicles and pustules; the face, the trunk, the extremities, and the scalp are involved. Lesions may appear both in covered and uncovered areas. Lesions may be seen on the palms and the soles. Necrosis, petechiae, and ulceration may be features and pruritus may also occur. Pain is unusual, and, if it occurs, it is often associated with secondary bacterial infection. In patients who have been previously vaccinated against smallpox, a milder form of disease occurs. In children, the lesions may appear as nonspecific, erythematous papules that are 1-5 mm in diameter and suggestive of arthropod bite reactions. The lesions of monkeypox need to be differentially diagnosed with that of small pox and chicken pox, technically only chicken pox as small pox has been eradicated [28].

5. Clinical and Laboratory Diagnosis

The geographic location of the patient is important in the diagnosis of monkeypox, as the disease usually occurs in remote villages in the tropical African rain forests. Differentiation from chickenpox is important; the latter appears in successive crops so that lesions at various stages of development are visible at any time. In contrast with smallpox, the distribution of chickenpox is 'centripetal' with more lesions on the trunk than on the face and extremities. For definitive diagnosis, scabs can be forwarded to a reference laboratory where electron microscopy may confirm the presence of an *Orthopoxvirus* and differentiate this virus from varicella virus. The virus can be cultured in tissue culture and identified by DNA restriction analysis.

A viral culture should be obtained from an oropharyngeal or nasopharyngeal swab. A skin biopsy specimen of the vesiculopustular rash or a sample of the roof of an intact vesiculopustule should be analyzed. Tissue for PCR of DNA sequence-specific for the monkeypox virus may be obtained. Paired sera for acute and convalescent titers may be analyzed. Serum collected more than 5 days for IgM detection or serum collected more than 8 days after rash onset for IgG detection was most efficient for the detection of the monkeypox virus infection [29]. A Tzanck smear can help differentiate monkeypox from other nonviral disorders in the differential diagnosis. However, a Tzanck smear does not differentiate a monkeypox infection from smallpox or herpetic infections.

Monkey pox cases were confirmed based on virus isolation or detection of the virus by polymerase chain reaction (PCR) from a clinical specimen (skin biopsy or throat culture). Individuals who presented with fever and rash within 21 days of exposure to monkey pox and had serum positive for orthopox immunoglobulin M (IgM), but did not have culture- or PCR- positive clinical specimens, were classified as having a probable case of infection [29,30]. The most reliable clinical sign differentiating monkeypox from smallpox and chickenpox is enlarged lymph nodes, especially the submental, submandibular, cervical, and inguinal nodes. Regarding exanthema, nonspecific lesions and inflammation of the pharyngeal, conjunctival, and genital mucosae have been observed [28].

5.1. Histological Findings

Histological examinations of papular lesions could show the presence of acanthosis, individual keratinocyte necrosis, and basal vacuolization, along with a superficial and deep perivascular, lymphohistiocytic infiltrate in the dermis. Lesions in the vesicular stage could show spongiosis with reticular and ballooning degeneration. Multinucleated epithelial giant cells can be another

significant observation. Pustular lesions might show epidermal necrosis with numerous eosinophils and neutrophils, many displaying karyorrhexis. Necrosis may extend through full-thickness epidermis with sharp lateral demarcation from adjacent intact epidermis. The associated perivascular infiltrate may include eosinophils and neutrophils in addition to lymphocytes and histiocytes and petechial lesions can demonstrate secondary vasculitis. Amphophilic intranuclear structures suggestive of viral inclusions may also be seen in keratinocytes [28].

Immunohistochemistry staining for Orthopox viral antigens is available and can be performed in select reference laboratories. Electron microscopic observation can reveal intracytoplasmic, round-to-oval inclusions with sausage-shaped structures centrally, measuring approximatrely 200-300 µm. These Inclusions were noted to be consistent with Orthopox viruses, permitting differentiation from Parapox and Herpes viruses [28].

6. Treatment

The Centers for Disease Control and Prevention (CDC) recommended smallpox vaccination within 2 weeks, ideally before 4 days, after a significant, unprotected exposure to a diseased animal or a confirmed human case [31]. Data from the African outbreaks suggest that prior smallpox vaccination confers 85% protection from monkeypox viral infection. Efficacy of vaccination was noted to be prolonged with protection noted even several years after vaccination, and the incidence of complications being reduced [8].

Since human infection with monkeypox virus is a rare disease, no benefit would be derived from vaccination with Vaccinia virus. Furthermore, smallpox vaccination cannot be undertaken in populations with high prevalence of HIV infection because of the risk of serious complications. Antiviral chemotherapeutic treatment is not a viable option in those remote places where the disease is likely to appear. The treatment would have to be administered in the very early stages of the disease and it is unlikely that the treatment could be made available in time. In addition, the treatment is not devoid of side effects [32].

7. Prevention and Control

Improved infection control measures, including the regular screening, and isolation of newly infected animals will certainly help in preventing outbreaks among animals. Better hygiene habits are warranted to avoid spreading of the virus on fomites which then become a source for newer infections. Vaccination with vaccinia virus could be choice to protect animals. Because infections have been reported in Asian monkeys mixed with primates from Africa, care must be taken to house these species separately. Anyone who has been exposed to monkeypox virus should avoid contact with animals, particularly rodents and non-human primates, to stop transmitting the virus [32].

During an outbreak, monkeypox viral spread may be controlled by quarantining (at least for 6 weeks from the date of the last exposure) the infected animals and tracing of their contacts. Areas where these animals have been kept should be cleaned and disinfected thoroughly. Adherence to specific instructions from the state or local health department or the CDC Web site is required.

8. Recent Advances in the Knowledge of Monkeypox Virus

A recent study has observed that the presence of a gene coding for Golgi-associated retrograde protein (GARP) complex in an infecting monkeypox virus strain could contribute to serious infection. The same study has also noted that it is important to identify the host target cells which are required for viral multiplication could pave the way for development of anti-viral therapy [33]. Another report recently noted that it was not exactly known as to how the monkepox virus spreads to humans. The same research study has suggested that, although there is no known reservoir for monkeypox virus, a close association with wild animals leading to bites, and consumption of bush meat could be potential risk factors to acquire monkepox virus infection [32]. Immunization with highly attenuated smallpox strain proved to be beneficial in human giving a protection for up to 6 weeks after vaccination. The same study has observed that such highly attenuated smallpox vaccine could provide longer protection for more than a year as observed in monkeys [33]. Identification of infection with monkeypox virus is complex due to its similarities between smallpox virus, and, varicella-zoster viruses. Recently a study has evaluated utility of two methods that included the real-time quantitative polymerase chain reaction (PCR) assay, and the more automated GeneXpert MPX/OPX technique in the laboratory diagnosis of monkeypox [35,36]. Development of an on-site laboratory diagnostic test which can be used both in humans and animals was recently reported. It is an immune-filtration technique called as ABICAP (Antibody Immuno Column for Analytical Processes). This works on a gravity-driven flow-through antigen capture ELISA, different from the traditional enzyme linked immunosorbent assays (ELISAs), and the lateral flow Immunochromatographic tests [37,38].

9. Conclusion

Among the group of pox viruses, the smallpox virus has been declared as non-existent in the wild many years back. Although Varicella-Zoster virus/Chicken pox virus, the causative agent of chicken pox is prevalent among humans, it is a self-limiting infection. The cause of concern now is the presence and potential spread of other hither to less known pox viruses, including the monkeypox in humans. 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. In the era of globalization, there is a frequent mobility of human, carrying a potential for spread of monkeypox. Cross border transport of animals also provides an imminent threat of spread of infection. Biological warfare and potential threat of bioterrorism cannot be ruled out; therefore, a

better understanding of monkeypox virus and similar microorganisms could contribute to better management of emergency situations.

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