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MONKEYPOX AND ITS CURRENT REALITY

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ABSTRACT

Introduction: *Monkeypox or "Monkeypox" is a species of poxvirus, which possesses double-stranded DNA. This species has the potential to be used as bioterrorism; and currently has re-emerged in non-endemic countries.*

Objective: *To detail the current information related to monkeypox and its epidemiological repercussions; in addition, to analyze the management and prevention of the contagion of this disease.*

Methodology: *a search was carried out in PubMed, Elsevier and Google Scholar, with the terms Monkeypox, Ape Pox and Monkeypox. Some articles were rejected due to lack of relevance.*

Results: *Monkeypox is transmitted by nasopharyngeal, oropharyngeal or intradermal routes; it has an incubation period of 5 to 21 days. Its diagnosis is made by laboratory tests such as PCR-RT and biopsy of skin lesions. Prevention is carried out with vaccines (especially the Ankara vaccine), which is 85% effective. Other drugs can be used in case of infection by this virus; however, their efficacy has not been determined so far. Currently, third generation vaccines are being developed.*

Conclusions: *Monkeypox had its outbreak in the 1970s and re-emerged in 1990. In 2020, 5257 suspected patients were found. It has now been discovered in the United Kingdom, Israel, United States, Singapore, among others. Current management is symptomatic and prevention with vaccines. The administration of Tecovirimat and Brincidofovir have controversial efficacy. Vaccines have shown greater effectiveness.*

KEY WORDS: *Monkeypox, orthopoxvirus, smallpox, Polymerase Chain Reaction, Poxviridae infections.*

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INTRODUCTION

Within the poxvirus family there are several types of viruses with similar DNA that infect many vertebrate hosts, among these viruses are the orthopoxviruses. Some infections caused by orthopoxviruses such as zoonotic monkeypox virus also called monkeypox and variola cause fatal consequences in humans(1,2).

With the global decline of smallpox in the 1980s, monkeypox took the place of the most important orthopoxvirus for public health. Therefore, the global commission for the certification of smallpox eradication recommended research and surveillance for monkeypox and also for other orthopoxvirus infections. Forty years after that report we have a worldwide increase in reported cases of the disease(3-5).

The so-called monkeypox takes its name from the fact that it was isolated for the first time in these primates, although the main reservoirs of its particles are rodents. The disease produced by this poxvirus originates from Africa where there is direct contact with the reservoir, causing a systemic picture with vesicles, fever and lymphadenopathies; however, in 2003 we had the first outbreak in the western hemisphere(1,2,4,5). Currently, the simian virus has re-emerged in different regions of the world, including South America, and consequently it has entered the world public health agenda due to the possibility of being a potential agent of bioterrorism(3). Below we will briefly describe simian pox, its etiology, epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment and discuss the critical need for further research to address this public health challenge.

The species of monkeypox virus also called monkeypox belongs to the poxviridae family. This is a diverse and large family of double-stranded DNA viruses that multiply in the cytoplasm of infected cells. They have all the proteins necessary for replication, transcription, assembly and genome output but require host ribosomes for mRNA translation(4,6,7).

They belong to the subfamily chordopoxvirinae and to the genus orthopoxvirus according to the shared antigenic similarity, the induction of cross immune protection and phylogenetic grouping. In electron microscopy, simian pox virus is seen as ovals or bricks enveloped by comparatively large lipoproteins of 200-400 nanometers (3,5,6).

Simian pox is a reemerging zoonotic disease threat. In 1958 Copenhagen, Denmark, it was first revealed among Asian monkeys originating from Singapore, 2 weeks after importation. Although it was first recognized in captive monkeys, data suggest that rodents and other small mammals are the natural reservoir. This zoonotic disease is endemic to Central and West Africa. The first reported case was in Zaire in 1970, present-day Republic of Congo, in a 9-month-old boy. Since that time there have been occasional outbreaks in human populations, and infections have also been demonstrated in rats, mice, prairie dogs, monkeys and squirrels(3-6,8).

Since 1970, the number of human cases has increased, especially in the Republic of Congo, and the median age of manifestation has also increased from 4 years in the 1970s to 21 years from 2010 to 2019(9). More than 80% of cases recorded from cohorts in 1970-1979, 1981-1986 and 1996-1997 were younger than 15 years, while less than 50% of the population was younger than 15 years at those times(10).

At this time, 2 genetically distinct clades have been identified, the West African clade located essentially in the West African Subregion and the Central African or Congo Basin clade located mainly in the Central African Region(3,6,9). The overall case fatality rate was 8.7 %, with a significant difference between clades: 10.6 % from Central Africa (95 % CI: 8.4 %- 13.3 %) versus 3.6 % from West Africa (95 % CI: 1.7 %- 6.8 %)(9). Other authors show that the West African clade has a case fatality rate of less than 1% and the Central African clade a case fatality rate of up to 11% in unvaccinated children (6). A systematic review shows that the smallpox vaccine has an efficacy of about 85% against monkeypox and reduces the frequency and intensity of clinical manifestations, with case fatality rates ranging from 0 to 11% (10).

In 2003, giant gambian rats brought from Ghana infected prairie dogs in the Midwestern United States that were sold as pets, subsequently leading to more than fifty human cases of simian pox. In October 2018, a case was reported in a male who traveled from Nigeria to Israel(11).

A male who traveled from Nigeria to Singapore also presented symptomatology in May 2019 and in May 2021, 3 members of a British family returning from their trip to Nigeria were infected with simian smallpox virus. In June and November 2021, 2 men traveling from Nigeria to Texas and Maryland, respectively, were reported. As of May 2022, an individual who returned to Massachusetts from Canada, as well as other possible cases in the United Kingdom and several non endemic countries in Europe and the Americas are being investigated and further investigations are underway to establish the likely source of infection and to restrict further spread (12-17).

Not being vaccinated against smallpox and living in rural or forested areas of central and west Africa have been shown to be risk factors for contracting the disease, in addition to preparing or handling wild animals and caring for someone affected by simian smallpox virus. In the absence of reports and confirmations of disease, the prevalence and incidence of human infection cannot be accurately defined, but both have increased since routine variola vaccination was discontinued(5,6,8,18).

Humans can contract the virus by respiratory droplets, body fluids, direct contact with skin lesions of infected patients, indirect contact with contaminated fomites, bites, scratches from carrier animals, direct contact with body fluids or lesions of infected animals. Therefore, isolation in a negative pressure room is recommended, and the necessary precautions should be taken during medical care(6,8,18,19).

METHODOLOGY

A total of 36 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which a total of 23 bibliographies were used because the

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previous 9 articles were not relevant for this study. The sources of information were PubMed, Google Scholar and Elsevier; the terms used to search for information in Spanish and English were: "Monkeypox", "Monkeypox virus", "Monkeypox vaccine", "Monkeypox epidemiology", "Monkeypox Management" and "Clinical cases of monkeypox". The choice of literature exposes elements related to the evolution of monkeypox in the last 5 years; in addition to this factor, these studies have several important factors related to their different treatment routes and different ways of contact with patients according to the clinical cases mentioned in this review.

DEVELOPMENT

Simian pox virus can enter through the oropharynx, nasopharynx or intradermally through direct contact with lesions. This virus usually replicates at the site of inoculation and then travels to local lymph nodes. Initial viremia leads to viral shedding and subsequent organ seeding and the incubation period usually lasts between 7 to 14 days with a longer limit of 21 days(6).

Secondary viremia and the onset of symptoms such as fever and lymphadenopathy usually appear as prodromal symptoms 1 to 2 days before lesions appear. It is at this precise moment that the infected person can infect others. Subsequently, lesions usually appear on the skin and in the oropharynx(6).

Other authors agree with the incubation period of monkeypox being between 5 to 21 days, followed by clinical signs of up to 21 days(3,15). They show that transmission occurs by secretion of fluids, generally from the respiratory tract or skin lesions(15).

Symptoms are usually self-limited and are divided into an invasion phase presenting fever, lymphadenopathy, myalgia, chills, headache and lethargy; and a rash phase that usually begins between day 1 and 3 after the onset of fever, generally located on the face and extremities, also affecting mucous membranes, genitals, palms and soles. Symic smallpox can be differentiated from other types of diseases such as chickenpox, measles and smallpox by the presence of lymphadenopathy. Eruptions begin as macules progressing to papules, vesicles, pustules and crusts that later dry and fall off. Crusts of dry lesions may increase the risk of transmission. The number of lesions varies from a few to thousands of lesions, being more lethal in young children(3,12,20).

Nguyen PY et al, in their study on the resurgence of human monkeypox and the decrease of population immunity in the context of urbanization, show the following classification of cases that we find convenient to share.

Table 1. Classification of monkeypox cases.

Term	Concept
Suspect case	Acute disease with fever >38.3 °C, asthenia and intense headache, back pain, myalgia and lymphadenopathy that after 1 to 3 days continues with progressive rash usually on the face that then spreads to other parts of the body, and may affect soles and palms.
Probable case	Clinically compatible case not confirmed by laboratory with epidemiological link to a confirmed case.
Confirmed case	Clinically compatible case confirmed by PCR, positive IgM or virus isolation.

Source: Nguyen PY et al, Reemergence of Human Monkeypox and Declining Population Immunity in the Context of Urbanization (21).

A definitive diagnosis of monkeypox can only be established by laboratory testing. For this purpose, the World Health Organization (WHO) recommends smears of exudate from vesicular lesions or scabs stored in a dry, sterile, non-viral transport medium and cold test tube(20).

Among the main differential diagnoses of simian pox are smallpox, generalized vaccinia, disseminated zoster, varicella, herpetic eczema, disseminated herpes simplex, yaws, scabies, syphilis, measles, drug-associated rash and skin infections(1,6).

Treatment is generally symptomatic and supportive; at the time of writing this research there is no specific antiviral drug approved, which emphasizes the importance of using preventive measures that can reduce the incidence of outbreaks. Therefore, the infected individual should be isolated, wear a surgical mask and keep the lesions covered as much as possible until the scabs of the lesions have fallen off naturally and a new layer of skin has formed(3,6).

Vaccines have been improved since the eradication of smallpox. First generation smallpox vaccines were disseminated in calfskin and purified from calf lymph. Second-generation vaccines were disseminated in tissue cell culture using good modern production practices, reducing the risk of contamination, but both first- and second-generation vaccines pose a risk of adverse events because they contain replication-capable vaccinia

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virus. Third generation vaccines are also disseminated in tissue culture with good and modern production practices, however, they use attenuated vaccinia viruses with favorable safety profiles(22,23).

The U.S. Food and Drug Administration approved the first drug, tecovirimat, to treat smallpox (under the Animal Standard) but its efficacy has not been determined due to the lack of human cases of smallpox(3). The oral DNA polymerase inhibitor brincidofovir, the oral intracellular viral release inhibitor tecovirimat and the intravenous immunoglobulin vaccinia maintain unknown efficacy against simian smallpox virus(6,24).

The modified vaccinia Ankara vaccine (MVA) has been used for the prevention of monkeypox, based on the premise that a vaccine against monkeypox poxvirus could also protect against other orthopoxviruses, clinical trials have shown that this vaccine is reliable and that it stimulates the creation of antibodies in immunocompromised patients and those with atopy (3).

Similarly, the third-generation IMVAMUNE vaccine, also used against smallpox, has been tested in HIV-infected persons and in individuals with atopic dermatitis, showing safety and immunogenicity and protection against simian smallpox in some animal studies(22).

In the United States of America, the second-generation ACAM2000 vaccine was licensed for use during an emergency, where vaccination was also suggested for laboratory and health care personnel (22).

According to the Centers for Disease Control and Prevention, vaccination against monkeypox within the first four days of exposure is successful in preventing disease manifestation, whereas vaccination within 14 days is successful in reducing the severity of the disease, but further data collection and analysis is required to determine the advantages and disadvantages of preventive vaccination against monkeypox (3,6).

Third-generation vaccines are still in development and remain unlicensed in the United States. However, some have already completed several preclinical and clinical studies and can be used with an emergency use approval (22).

The epidemiology of simian smallpox has been variable since its discovery in 1970, ranging from 48 cases in 1970 to 520 cases discovered in 1990. Such is the importance of analyzing its epidemiology that in 2020, 6257 suspected cases of monkeypox were identified. Another important point of analysis is that the transmission from rodent to rodent became a transmission from animal to human, producing an outbreak of 47 cases, between confirmed and probable. Among the possible explanations for the resurgence of monkeypox, it is theorized that reduced immunity, and to a lesser extent deforestation, are the causes (3,9,25).

Another important point is that human-to-human transmission has been caused by contact with respiratory droplets and contact with contaminated patient fluids, the patient's environment or objects (26,27).

Currently, from the period 2018 to 2021, 6 people who have traveled from Nigeria, have been diagnosed with Simian Pox in non-African countries: 4 in the United Kingdom, 1 in Singapore, and 1 in Israel. A UK study tested 7 patients infected with Simian Pox from the period 2018 to 2021 (16,28). 4 patients were male and 3 were female; e patients acquired the virus in the United Kingdom, 1 was a health care worker who acquired the virus nosocomially, and 1 who acquired it abroad, transmitted it to an adult and a child in his or her household. Five of the seven patients were hospitalized for 22 to 39 days due to persistent PCR positivity. 3 patients were treated with Brincidofovir at a dose of 200 mg once a week, with the consequence of elevated liver enzymes, which resulted in discontinuation of the drug. 1 patient was treated with Tecovirimat at a dose of 600 mg every 12 hours for 2 weeks, where no adverse effects were evidenced and the duration of the disease was 10 days compared to the other 6 patients. One patient showed a mild relapse 6 weeks after medical discharge(29).

In a case of a 24-year-old male patient who arrived in the United States from Nigeria, he presented within 24 to 48 hours with characteristic symptoms of burning sensation on the skin, with vesicles on the forehead and nose, which spread to the arms and trunk; he also presented fever, chills and headache. Physical examination revealed lymphadenopathy at right cervical level and pustules with an erythematous base and central umbilication at facial level, neck and hands in greater prevalence. In the oral mucosa, erosions were evidenced and in the lower labial mucosa, an intact pustule was evidenced. As a background, Acyclovir was administered due to a varicella zoster infection. During hospitalization, no new lesions were evidenced. A biopsy of the pustules on the abdomen was performed, showing epidermal necrosis, reticular degeneration and vesiculation. Therefore, with these findings and the history of the trip, the suspicion of monkeypox was reached. A PCR-RT culture was performed and the presence of this virus was confirmed. In the end, symptomatic medication was administered, in addition to isolating the patient in a room along with the use of protective equipment for health care workers. These researchers concluded that vaccination is of vital importance for secondary prevention, since it provides 85% protection against monkeypox. In addition, they mention that post-exposure prophylaxis should be performed in patients with high-risk contact within the first 4 days to a maximum of 14 days after initial contact (13).

Several animal studies were performed to demonstrate the evidence of Brincidofovir at doses of 5 mg/kg or 20 mg/kg and its measurement at plasma level. However, it was demonstrated that there are no detectable concentrations with any of the doses mentioned and in maintained doses of 20 mg/kg it produced gastrointestinal toxicity; therefore, the drug was given at doses of 20 mg/kg and 5 mg/kg was administered in 48 hours and 5 mg/kg was administered 48 hours later, obtaining a favorable response. In addition, it was demonstrated that early administration before infection with simian smallpox had a survival rate of 57%; those who were administered the drug

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when they had already been infected had a survival rate of 43%, and 29% when they received the treatment 1 day after infection with simian smallpox. The immune response is usually evident when the animals present cutaneous lesions, which is usually between day 9 to 13 after infection; furthermore, when administering this drug, there were no differences in relation to the immune response(30).

CONCLUSIONS

The epidemiology of monkeypox has been variable since its discovery in 1970. Rodent-to-rodent transmission evolved into animal-to-human transmission. Human-to-human transmission has been through contact with respiratory droplets and contact with contaminated patient fluids, the patient's environment or objects. A definitive diagnosis of monkeypox can only be established by effective laboratory testing. The oral DNA polymerase inhibitor brincidofovir, the oral intracellular viral release inhibitor tecovirimat and the intravenous immunoglobulin vaccinia maintain unknown efficacy against simian smallpox virus. The use of modified vaccinia vaccinia Ankara and IMVAMUNE have shown safety in animal research for the prevention of monkeypox, based on the premise that a vaccine against monkeypox poxvirus could also protect against other orthopoxviruses, but third-generation vaccines are still under development. Vaccination, which is of vital importance for secondary prevention, provides 85% protection against monkeypox. Post-exposure prophylaxis is recommended in patients with high-risk contact within the first 4 days to a maximum of 14 days of initial contact.

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