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Review

Epidemiology, Clinical Manifestations, and Diagnosis of Monkeypox

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Abstract

Monkeypox is an evolving zoonotic disease which is caused by the monkeypox virus. In the recent times the number of cases across the globe has increased. The disease was previously endemic to Africa but is now spreading worldwide. More than 62,000 cases were reported across 104 countries. The illness typically has an incubation period of 7 to 14 days and symptoms such as fever, headache, fatigue, myalgia, generalized body aches, lymph node enlargement, and skin lesions are common. Monkeypox is similar to smallpox, but lymphadenopathy is the characteristic feature of monkeypox. Due to the numerous illnesses that can produce skin rashes, it may be challenging to distinguish monkeypox solely based on clinical presentation hence individuals suspected with monkeypox infection should be tested for the virus. Diagnostic tests are essential for determining the presence of an orthopoxvirus infection. When these tests are paired with clinical and epidemiological data, such as a patient's history of vaccinations, they are most effective. Surface lesions and/or skin materials like crusts and exudate swabs are good samples for diagnosis. Nucleic acid amplification testing, such as real-time or classical polymerase chain reactions, is used in the laboratory to confirm specimens from suspected cases. Clinical and epidemiological data should be taken into account when monkeypox infection is confirmed. Further research is needed to develop preventive strategies to minimize the spread of the disease. The purpose of this research is to review the available information about an epidemiology, clinical manifestations, and diagnosis of monkeypox.

Keywords: monkeypox, endemic, orthopoxvirus, zoonotic disease, epidemiology

Introduction

The monkeypox virus (MPXV), an orthopoxvirus that belongs to the Poxviridae family of viruses, is responsible for causing monkeypox which is a zoonotic viral disease. The disease is termed monkeypox since MPXV was originally discovered in 1958 in laboratory monkeys transported from Singapore. However, rats and other small animals are more likely to be the MPXV's natural hosts. The variola virus, which is the cause of smallpox, is another member of the genus Orthopoxvirus. Human monkeypox symptoms are quite comparable to smallpox symptoms, but with a lower death rate. The MPXV first appeared in humans in sporadic occurrences in many African nations in the 1970s, but over the past 20 years, the virus has spread more widely over the continent of Africa (1). Monkeypox incidences outside of Africa are rare and often connected to foreign travel or animal trafficking, as per the epidemiological characteristics and geographic distribution of the disease. The coronavirus disease 2019 pandemic and the rising number of confirmed instances of human monkeypox, which have been reported from numerous nations in non-endemic areas since May 2022, together constitute a public health emergency of international concern. The majority of documented cases of monkeypox do not appear to be connected to known contact with infected people or endemic travel, suggesting that this most recent multi-country outbreak is behaving in an atypical manner (2).

With signs and symptoms lasting two to four weeks and an eight-day incubation period, monkeypox is a self-limiting illness. a viral febrile prodromal phase is marked by headache, malaise, backache, exhaustion, lethargy, and low-grade fever, the earliest signs and symptoms are typically non-specific. A vesiculopustular rash then develops 12–16 days after exposure and starts on the face and trunk before centrifugally spreading to other body areas, such as the palms and soles. Macular, papular, vesicular, and pustular lesions are the stages through which rash morphologically proceeds. The pustules eventually develop crusts, which, after one to two weeks, desquamate. The initial signs and symptoms of MPXV infection resemble smallpox, however unlike smallpox, lymphadenopathy is a significant hallmark, with sensitive maxillary, cervical, and inguinal lymphadenopathy, detected in 84% of unprotected individuals, and 54% of patients who had received vaccinations. Lymphadenopathy suggests that MPXV may be subject to a more active immune response and identification than variola (3).

Monkeypox infection is diagnosed by using a variety of techniques, including electron microscopy and immunohistochemistry, on the tissue removed from the lesion to identify MPXV. Since real-time polymerase chain reaction (PCR) is a highly efficient and sensitive method for detecting viral DNA, it can also be used to track the virus in a sample. To determine previous exposure to an orthopoxvirus, whether through infection or vaccination, serological markers such as antiorthopoxvirus immunoglobulin M and immunoglobulin G can be employed (4). Diagnostic tests are crucial for determining the presence of an orthopoxvirus infection. When these tests are paired with clinical and epidemiological data, such as a patient's history of vaccinations, they are most effective. Conventional tests including virus isolation from a clinical specimen, electron microscopy, and immunohistochemistry are still valid methods, but they need complex lab equipment and highly skilled technicians. However, real-time PCR is very sensitive and effective at finding viral DNA (5). The purpose of this research is to review the available information about an epidemiology, clinical manifestations, and diagnosis of monkeypox.

Methodology

This study is based on a comprehensive literature search conducted on November 21, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about Epidemiology, clinical manifestations, and diagnosis of monkeypox. There were no restrictions on date, language, participant age, or type of publication.

Discussion

The first instance of monkeypox was documented in 1958 among monkeys housed for research, hence the name monkeypox is attributed to the disease. In the Democratic Republic of the Congo, the first instance of monkeypox in a human was noted in 1971. However, the first case outside of Africa was found in the United States in 2003 and was linked to contact with pet prairie dogs who were infected. The human MPXV, a double-

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stranded DNA virus that belongs to the Poxviridae family and the orthopoxvirus genus, is one of the four orthopox virus species that may infect people. The other three, which together cause smallpox, which is currently eradicated, are the cowpox virus, variola minor virus, and variola major virus. West African and Central African are the two genetic subclades of MPXV. These two clades differ geographically, and this is accompanied by diverse epidemiological and clinical characteristics. The Congo Basin clade has a case mortality rate of roughly 11% and a recorded human-to-human transmission, in contrast to the West African clade, which has a case fatality rate of less than 1% and no record of human transmission (6).

Epidemiology

Beer and Rao stated in their study that human monkeypox outbreaks were recorded in the Democratic Republic of the Congo (DRC), Central African Republic, Cameroon, Republic of Congo, Liberia, and Nigeria between August 2017 and August 2018. The literature has proposed and provided evidence for a progressive rise in monkeypox case counts between 1980 and 2013, although it is unclear to what extent recent outbreaks reflect this trend. In addition, the recent apparent rise in reports of monkeypox in various places raises concerns about a change in the epidemiological trend. Most age-related data were gathered from the DRC, where children regularly accounted for the majority of caseloads. Approximately less than 50% of the population was under the age of 15 in the 1970–1999, 1981–2006, and 1996–2007 cohorts, yet more than 80% of cases were under this age. Since 1970, the median age of cases has been gradually rising. Age-related data outside of the DRC were scarce and contradictory. Early outbreaks mostly affected children under 10 years old, but other trends showed higher median ages for fewer numbers of cases. In the latest outbreak in Nigeria, the median age of the 228 probable cases was 30. In 18 of the 26 reports where gender information was provided, more male cases than female cases were reported (7). Map of countries with suspected number of cases is illustrated in **Figure 1.**

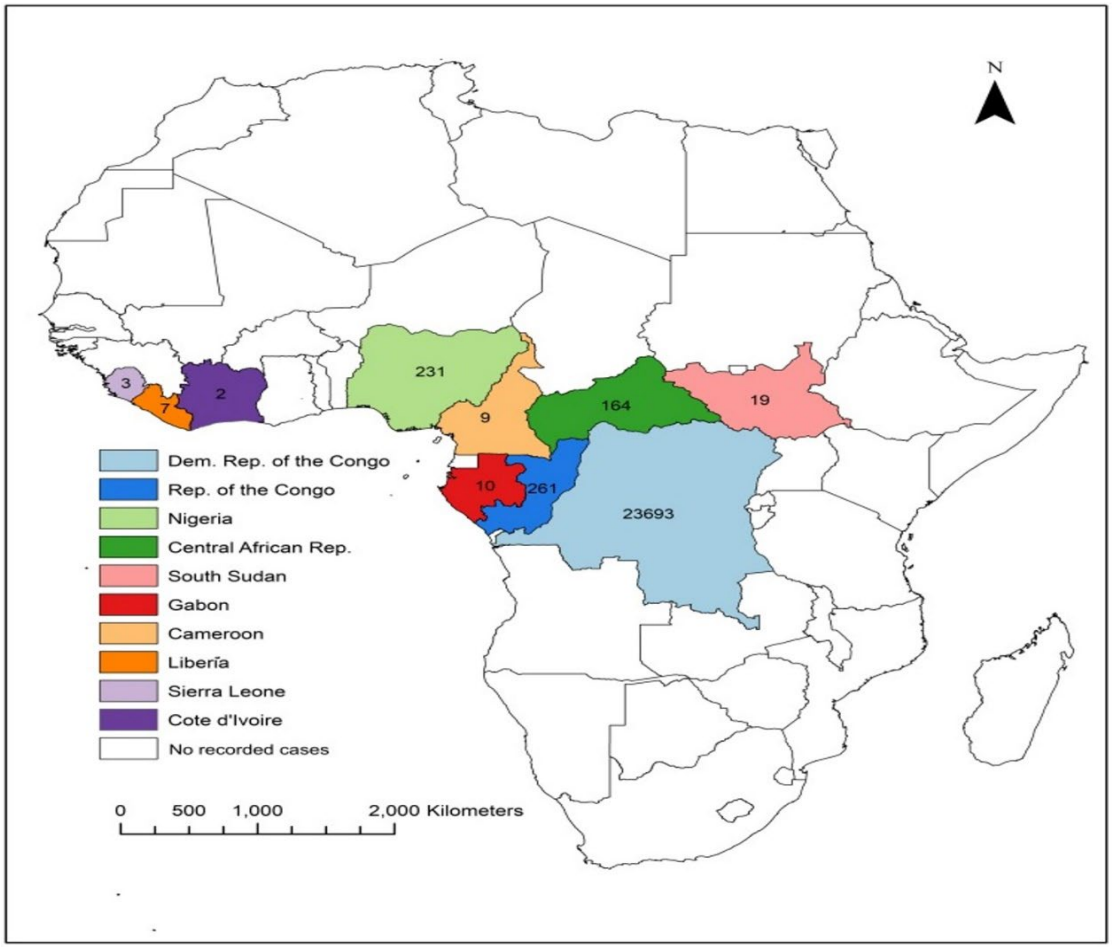

Figure 1: *Map of countries with suspected number of cases of monkeypox (7)*

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Thornhill et al. reported 528 cases between April 27 and June 24, 2022, in 43 locations across 16 countries in their findings (8). Results of a systematic review depicted that since the 1970s, there have been more instances of human monkeypox, with the DRC experiencing the largest rises. The average age at presentation rose from 4 in the 1970s to 21 in the present day. A substantial variation between clades was found in the case fatality rate, which was 8.7% overall but 10.6% in Central Africa and 3.6% in West Africa. Since 2003, outbreaks have occasionally been caused by import- and travel-related dissemination outside of Africa. Activities or interactions with diseased people or animals pose a risk of contracting monkeypox. Monkeypox cases are increasing, especially in the highly endemic DRC, spreading to other nations, and the median age is shifting from young children to young adults (9). The first cases outside of Africa were discovered in the United States in 2003, yet monkeypox continued to be a neglected worldwide public health problem. MPXV was found to be the cause of some Midwesterners' fever, rash, respiratory problems, and lymphadenopathy after an outbreak investigation and connected the symptoms to contact with pet prairie dogs. It quickly spread. During the outbreak, cases of monkeypox were documented in six states: Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin (10).

The incidence of monkeypox infections has substantially increased after two cases of the virus being acquired by travellers from Nigeria to the USA. This raised the alarm about the virus's ability to spread across the USA. More than 1,500 cases have been documented by June 10, 2022, across 43 nations, including those in Europe and North America. Although the MPXV is common in central and western Africa, there are worrying signals that it may be spreading globally due to its presence in the developed world (11). Ilic et al. reported in their study findings that more than 62,000 cases of human monkeypox were reported in 104 countries around the world between 13 May 2022, when the first verified case in the United Kingdom occurred, including 97 nations where the monkeypox disease was not endemic. In this worldwide outbreak, 20 people have passed away as of right now. Currently, the monkeypox outbreak is spreading alarmingly in several nations and poses a significant threat to global public health (12).

Clinical manifestations and diagnosis

The disease begins with a 1–4-day febrile prodrome that is accompanied by headache, backache, and muscle aches. Sometimes it is also accompanied by weariness, sweating, and lethargy, as well as the cutaneal presentation almost 1-3 days following the onset of a fever, skin rashes start to appear and then spread. Rash may occasionally appear first then leading to subsequent symptoms. Lesions start off as a flat rash a macula, then they rise up from the skin papules, and finally they fill with clear liquid to have a vesicle appearance. Pustules develop when the clear liquid inside the vesicles turns yellow. With the crusts falling off, pustules, crusts, and lesions vanish although the quantity of lesions varies. Patients are regarded as non-infectious once the crust has fallen off. People with weakened immune systems exhibit more severe illness symptoms. More severe side effects, such as respiratory distress and bronchopneumonia, can develop. Scarring from the rash is the result of an infection that occurs most frequently. Ocular infections can happen and may cause corneal scarring and even irreversible vision loss, and more severe complications and sequelae have been reported to occur more frequently in unvaccinated patients than in vaccinated ones. A characteristic feature that distinguishes monkeypox from smallpox is lymphadenopathy. This usually happens when the fever starts, a day or two before the rash starts, or very infrequently when the rash starts. In particular, the submental, submandibular, cervical, and inguinal lymph nodes frequently expand. Additionally, those who have been exposed may experience a rash on their mouth mucous membranes, a sore throat, and/or a cough (13).

Patel et al. revealed in their study that while 86.3% of the individuals reported having a systemic illness, all of them exhibited mucocutaneous lesions, most frequently on the genitalia or in the perianal region. Fever, lymphadenopathy, and myalgia were the most typical systemic signs and symptoms. Almost 61.5% of patients had systemic symptoms before the start of mucocutaneous manifestations, while 38.5%, 13.7%, and 36.0% only had mucocutaneous symptoms. Other symptoms included rectal pain, sore throat, and penile oedema. While 4.6% of individuals had tonsillar symptoms and 13.7% of participants had oral lesions, 35.9% of participants had concurrent HIV infection, and 31.5% of those who were examined for sexually transmitted infections had concurrent sexually transmitted infections (14). Goyal et al. described that the MPXV can take five days to three weeks to fully incubate. High-grade fever, chills, weariness, lymphadenopathy, muscle discomfort, and vesicular eruptions with a rash are all symptoms of monkeypox disease. All of the symptoms are present during the prodromal phase, but there is no rash. There are four to

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five days in the prodromal phase. Usually, the rash begins four to five days after the fever ends and lasts for two to three weeks. On the other hand, some people may develop the rash without experiencing the prodromal stage. Although the face is where the rash usually occurs, it can also affect the palms of the hands and the bottoms of the feet. The involvement of the genitalia, anus, and oral mucous membranes is present in recent cases of monkeypox infection (15). Oral and skin lesions among monkeypox patients are illustrated in **(Figure 2).**

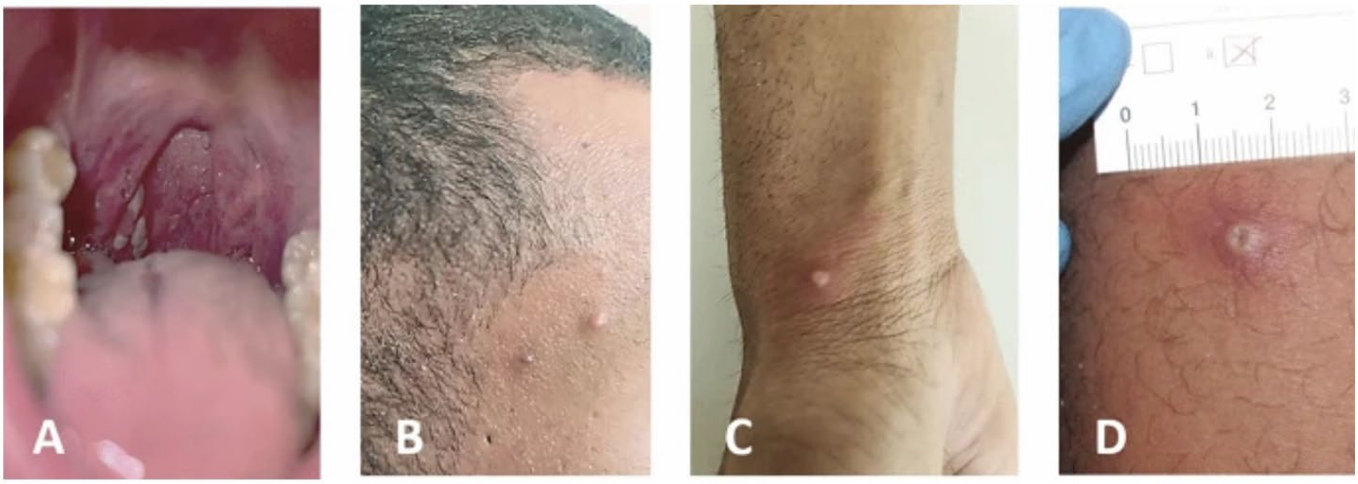

***Figure 2**: Oral and skin lesions among monkeypox patients (19)*

A thorough medical history that focuses on details including recent travel to an endemic region, receiving the smallpox vaccine, and connecting clinical information to the present symptoms can be very illuminating in determining the illness diagnosis, but it is insufficient to establish a conclusive diagnosis. The PCR is the premier diagnostic test. The viral DNA within the lesion persists constant for a considerable amount of time if stored in a dark and relatively cool environment, in addition to its great accuracy and sensitivity. Orthopoxviruses react cross-reactively in immunological tests. Even so, these tests might be helpful if there have been prior clues that point to the disease's origin. Immunoglobulin M is thought to be more successful at retroactively diagnosing newly infected patients than immunoglobulin G, despite the fact that immunoglobulin G alone cannot provide a conclusive diagnosis to a patient who has been exposed to the orthopoxvirus during his life through vaccination (16).

When determining the diagnosis, the clinical picture is useful. Due to the accuracy and sensitivity of PCR, the diagnosis is confirmed using this method. Vesicles, pustules, or dry crusts are the best places to collect samples from. It is important to carefully consider the patient's history, which should include the date that the fever started, when the rash started, when the specimen was collected, how the rash is doing right now, and the patient's age. Rapid patient screening with MPXV antigen detection at the point of care has been developed. More research is required to assess the yield of PCR from non-skin sites since the clinical importance in terms of reservoirs and transmission is still unknown given the disease's development and diversity in clinical manifestations (17). Other ulcerative sexually transmitted infections, such as genital herpes, syphilis, or chancroid, are differentially diagnosed as MPXV lesions, particularly when the genital and anal areas are the most affected places. The absence of the classic herpetiform figuration, in which the vesicles of genital herpes are frequently seen packed closely together, serves as a diagnostic marker. These lesions are unpleasant, unlike the syphilis chancre, and unlike chancroid, they first manifest as papules before developing into umbilicated and ulcerative sores (18). As the disease is no longer endemic and has the potential to spread regular genomic investigations, serological surveys, and evaluations for vaccination of health professionals and high-risk groups should all be done for monkeypox as part of normal disease surveillance protocols also further research shall focus on developing preventive measures to control the curb of disease timely.

Conclusion

Since monkeypox is no longer a rare condition, it is crucial improve the algorithm for determining the

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clinical spectrum and severity of monkeypox and evaluate the risk of transmission in relation to various types of contact with clinical cases. Additionally at all incident sites and high-risk geographical locations around the world, control and prevention measures should be put in place, including education and personal hygiene.

Disclosure

Conflict of interest

There is no conflict of interest

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Ethical consideration

Non applicable

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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