Monkeypox: A Review

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Abstract
Monkeypox is caused by a pox virus closely related to smallpox virus and spreads from animals to humans, and humans to humans following close contact. Prior smallpox vaccination gives partial protection against monkeypox. The steady increase in monkeypox cases in Africa over the past few decades were ignored by the global scientific community till this year, when more than 16,000 cases have been reported from nonendemic countries. Monkeypox has recently been labelled as a public health emergency of international concern by the WHO. While most of the current cases are in men who have sex with men, there is the larger threat of the disease spilling into the general population. The disease is characterized by a short febrile illness with lymphadenopathy followed by a rash which spreads centrifugally and passes through phases of macules, papules, vesicles, and pustules. Recovery occurs in most patients within 2–4 wk. Complications are more likely in children, pregnant women, and the immunocompromised. Specific diagnosis is by detection of viral DNA by PCR. Treatment is largely symptomatic. Tecorivimat is a promising antiviral drug. Vaccination with the currently available smallpox vaccines is recommended for high-risk groups, health care workers, and close contacts. Control of the monkeypox outbreak needs a multipronged effort comprising enhanced surveillance, quick diagnosis, isolation of affected people, ring immunization, and adoption of “one health” approach.

Keywords Monkeypox · Pox virus · Smallpox · Tecorivimat

Introduction

The world has not even recovered from the COVID-19 pandemic and there is this new threat of monkeypox looming ahead. There is an added concern that children may be severely affected. This article attempts to bring practising clinicians up-to-date with the salient features of this illness.

Etiology

Monkeypox (MPX) virus is an enveloped double stranded DNA virus belonging to Orthopoxvirus genus of the Poxviridae family [1]. It is closely related to smallpox but is of lesser severity. However, unlike smallpox, it also has animal reservoirs which have allowed it to survive and spread. The virus was first identified in 1958 in monkeys in Denmark [2]. The first human case reported was in 1970 in a child in Democratic Republic of Congo (DRC) [3]. Since then, monkeypox is endemic in Central and West Africa and two distinct clades have emerged—the Congo basin or Central African clade (clade 1) and the West African clade (clade 2). The former is more virulent with higher case fatality [4]. Being a DNA virus, major and frequent changes in the genetic structure are less likely for the MPX virus.

The disease is transmitted from both animals to humans, and humans to humans [1]. The natural reservoirs are monkeys, squirrels, Gambian pouched rats, dormice, nonhuman primates, and other species. Humans are infected by bite/scratch, close contact, and by eating inadequately cooked meat of infected animals. Transmission between humans is by large respiratory droplets, direct contact, and through contaminated fomites. The secondary attack rate among household contacts is less than 10%, unlike smallpox, where it was 35%–88% [5]. The role of direct sexual transmission is uncertain, but intimate skin and mucosal contact during
sex facilitates spread. Vertical transmission from mother to fetus or newborn leading to congenital MPX has also been reported [6].

**Epidemiology**

Cases have been reported from 10 African countries since 1970. A review summarizes the epidemiology of these cases between 1970 and 2019 [7]. DRC was the worst affected country where cases increased from 38 in 1970–1979 to 511 in 1990–1999, and 18,788 between 2010 and 2019. Nigeria was second worst affected with 181 cases followed by Republic of Congo (97 cases) and Central African Republic (67 cases). More than 90% of these cases had no history of smallpox vaccination. The median age of the infected increased from 4 y in 1970s to 21 y in 2010s. The pooled case fatality rate (CFR) was 8.7%. When separated by clade, the CFR of the clade-1 infections was 10.6% as against 3.6% for clade 2. While between 1970 and 1990s, all the deaths were in those below 10 y, children below 10 y contributed to only 37.5% of deaths in 2010s. The increase in cases in Africa is attributed due to waning of immunity following cessation of smallpox vaccination and increased encroachment of sylvatic areas for human activities. This increase in cases in Africa has been red flagged in literature for several years but largely ignored [8].

The cases outside Africa were first reported from the USA in 2003, when 53 people (median age 26 y, range 4–53 y) were affected with the West African clade following contact with pet prairie dogs who, in turn, were infected from exotic animals from Ghana [9]. Twenty one percent were vaccinated against smallpox. While 26% were hospitalized including one 10-y old with encephalitis; there were no deaths. Between 2018 and 2021, a handful cases with no fatalities have been reported from some countries (1 in Israel, 1 in Singapore, 7 in the UK); 5 were in returning travellers from Nigeria [7, 10].

On 6th May 2022, a case of monkeypox was reported from the UK in a traveller who had returned from Nigeria [11]. Since then, the number of cases have increased exponentially and in people with no history of travel to endemic areas. In the period between 1st January 2022 and 22nd July 2022, 16,016 laboratory confirmed cases of monkeypox and 5 deaths have been reported to WHO from 75 countries/territories/areas in all six WHO regions [12]. The five countries that have reported the highest cumulative number of cases globally are Spain (n = 3125), the United States of America (n = 2316), Germany (n = 2268), the United Kingdom of Great Britain and Northern Ireland (n = 2137). The African region has reported only 301 lab-confirmed cases but all the 5 deaths. However, the African surveillance network reported 1400 cases with 63 deaths in 2022 [13]. Considering the increasing number of cases across the world, the WHO declared MPX as public health emergency of international concern (PHEIC) on 23 July 2022 [14].

In a recently published multicountry study of 528 MPX infections (527 men and 1 woman) in 5 continents and 16 countries between 27 and 2022 and 24 June 2022, the median age of patients was 38 y (range 18–68 y) [15]; 98% of the people with infection were gay or bisexual men, 75% were white, and 41% had HIV infection. Notably 95% of HIV-infected individuals were on antiretroviral therapy, and the vast majority had undetectable viral loads. History of foreign travel was present in 28%, and coexistent STI were present in 29%. The major transmission was through sexual activity in 95% of the patients. In this study, MPX DNA was detected in 29 of the 32 people in whom seminal fluid was analysed; but whether this was a replication-competent virus was not established. Nine percent of the study patients reported prior history of smallpox vaccination. No deaths were reported.

In India, as on 24 July 2022, 4 cases of MPX were reported; the first case was reported on 14 July 2022. All four were men. The first three were from Kerala with a history of foreign travel but the last case from Delhi had no history of foreign travel [16].

Re-emergence of monkeypox in endemic and nonendemic areas has been attributed to changing biologic nature of the virus, climate change, waning immunity following cessation of smallpox vaccination coupled with increased international travel following the lifting of COVID-19 restrictions and high-risk sexual activity [17]. Phylogenetic analysis shows that MPX causing the current outbreak belongs to clade 3, which, in turn, is closely related to the virus causing the sporadic case in Maryland, USA in 2021, which, in turn, was related to the clade 2 viruses of Nigerian outbreak in 2017–2018 [18]. The genetic sequences of all the viruses of current outbreak are clustered tightly together suggesting a point origin of the outbreak.

While it is true that at this time that mainly adult homosexual males have been affected, the illness is likely to spread into the general population, women and children. Health care workers are at a heightened risk for infection. There is also concern about humans infecting animals, which may then serve as a recurrent source of infection [19].

**Clinical Features**

The incubation period ranges from 5 d to 21 d, typically 6–13 d [1]. All ages are affected but the median age has shifted upwards with passage of time [7]. Men are more
affected than females. Clinical features are similar to that of other pox virus infections including smallpox [20].

The prodromal phase is nonspecific and lasts generally for 0–5 d. It is characterized by fever, headache, lethargy, myalgia, and lymphadenopathy. The lymphadenopathy appears with onset of fever and may be unilateral/bilateral cervical, axillary, or inguinal. This is followed by the appearance of the rash which lasts for 2–4 wk. The lesions are polymorphic and painful till they become crusted [21]. The number of lesions may vary from one to hundreds. The stages in the development of the rash are:

- The enanthems in the tongue and mouth appear first.
- This is followed by macules starting from face spreading to arms, legs, palms, and soles (centrifugal distribution). This is unlike chickenpox where distribution is centripetal.
- The rash goes through macular, papular, vesicular, and pustular phases. Classic lesion is vesicopustular. All lesions in the person are similar in nature, unlike chickenpox, where multiple phases can be found at the same time. However, pleomorphic rash may be seen in vaccinated patients.
- The commonly involved sites in order of frequency are face (98%), palms and soles (95%), oral mucous membranes (70%), genitalia (28%), and conjunctiva (20%). Involvement of palms and soles is the hallmark of MPX.
- By the 3rd day lesions progress to papules and by the 4th to 5th day, lesions become vesicles (raised and fluid filled), and by the 6th to 7th day, lesions become pustular, sharply raised, filled with opaque fluid, firm, and deep seated. These may umbilicate or become confluent.
- By the end of the 2nd week, they dry up and crust over. The scabs remain for a week before falling off. The lesions heal with hyperpigmented atrophic scars, hypopigmented atrophic scars, patchy alopecia, hypertrophic skin scarring, and contracture/deformity of facial muscles following healing of ulcerated facial lesions.

The illness is self-limiting and resolves in 2–4 wk in majority. Factors that predispose to severe illness include younger age (children), underlying immune deficiencies including HIV infection and other chronic illnesses, and absence of previous smallpox vaccination. The complications include secondary infections, bronchopneumonia, sepsis, encephalitis, and involvement of the cornea with ensuing loss of vision. The case fatality rate ranges from 1% to 10% and varies with clade (discussed earlier), host factors, vaccination status, and access to care. In a case series of 282 patients from DRC, there were no deaths in people who had received smallpox vaccination, but was 11% in those unvaccinated [22].

In a recently published case series during the current epidemic, in the 23 persons with a clear exposure history, the median incubation period was 7 d (range: 3 to 20 d) [15]. The common systemic features preceding the rash included fever (62%), lethargy (41%), myalgia (31%), and headache (27%) and lymphadenopathy (56%). Ninety-five percent of the persons presented with a rash; around two-third of them had <10 lesions, 73% had anogenital lesions, and 41% had mucosal lesions. About 10% patients presented with a single genital ulcer. Unlike what was reported earlier, multiple types of lesions were noted in some patients at the same time. Severe anorectal pain due to anorectal lesions was the presenting feature in 11.5% of the patients; this has not been reported earlier. Thirteen percent were hospitalized. Most admissions were for pain management, reduced oral intake due to oral lesions, treatment of bacterial superinfections, and isolation. Three patients had serious complications: one epiglottitis and two myocarditis. All patients improved and there were no deaths.

There is only 1 case of a boy aged 10 y with MPX in the current epidemic reported from the Netherlands [23]. There was history of travel to Turkey immediately before appearance of skin lesions but no known contact with MPX. The family members were unaffected. There were a total of 20 lesions on the body but no systemic features or lymphadenopathy. The routine labs were unremarkable and monkeypox DNA was detected by PCR from lesions, throat and blood. It was Clade 3 lineage B.1 but unrelated to the viruses currently circulating in Amsterdam. The child recovered uneventfully. Source of infection remained unknown.

Vertical transmission of monkeypox can lead to fetal infection. In a series of 4 pregnant women from DRC with monkeypox, 2 had early miscarriages and 1 had a second-trimester fetal loss [6]. The stillborn had a generalized skin rash, and MPX virus was detected in the fetal tissue, umbilical cord, and placenta. It is notable that this was the more virulent clade 1; the effects of the clades 2/3 on fetus are unknown.

**Differential Diagnosis**

The most common differential diagnosis is chickenpox [24]. Monkeypox is characterized by long prodromal period, lymphadenopathy, centrifugal distribution of rash, and slower spread of lesions, unlike chickenpox, where the prodromal period is short, rash is centripetal in distribution, lymphadenopathy is absent, and the spread of rash is faster. Other differentials for MPX include hand, foot, and mouth disease, infected scabies, measles, drug eruptions, secondary syphilis, and molluscum contagiosum.
Laboratory Diagnosis [1, 20, 21]

The various laboratory methods available for diagnosis include viral isolation, immunohistochemistry in tissues, molecular diagnosis, electron microscopy, and serology. The molecular tests include RT-PCR, recombinase polymerase amplification (RPA), loop-mediated isothermal amplification (LAMP) technology, and restriction-fragment-length polymorphism (RFLP), etc. Real-time PCR (RT-PCR) test on samples obtained from skin lesions, throat, blood, and urine can be used for diagnosis of MPX with good sensitivity and specificity. However, these tests are expensive and not available commercially.

Specific IgG and IgM against MPX may be detected by enzyme-linked immunosorbent assay (ELISA) after 5 and 8 days of infection. However, these are genus-specific and do not differentiate between the various pox viruses. IgG can also be positive due to past exposure or smallpox vaccination. IgM is more specific than IgG. The Orthopox BioThreat Alert® (Tetracore, Rockville, MD) is a point-of-care diagnostic test that can directly detect pox virus antigens from the material taken from skin lesions. It is, therefore, useful in the field settings, but is less sensitive than PCR and cannot distinguish MPX from other pox viruses.

The Indian Government has released guidelines for diagnosis of patients with MPX. Samples including skin scrapings, EDTA blood, serum urine, and nasopharyngeal/oropharyngeal swab will be processed for orthopox genus-specific PCR. If positive, then the samples will be processed for MPX-specific PCR [21].

Treatment

Treatment of MPX is symptomatic and supportive including maintaining fluid and electrolyte balance, nutrition, symptomatic therapy with antipyretics/analgesics, early identification of secondary infections, and prompt treatment with appropriate antimicrobial agents [25].

There are limited antiviral drugs available for MPX. Cidofovir which acts by inhibiting the viral polymerase has in vitro activity against pox viruses. It is, however, very nephrotoxic. Brincidofovir (CMX-001) is modified cidofovir with lesser nephrotoxicity. However, no convincing benefit was reported with three UK MPX patients with brincidofovir [26]. Recently, the compound ST-246 or tecovirimat has been approved for treatment of orthopox virus infections including smallpox, cowpox, monkeypox, and vaccinia in USA, Canada, and Europe [25]. It acts by inhibiting the function of a major envelope protein and prevents the release of the virus from the cell and, thus, infection of other cells. It has demonstrated efficacy in protecting animals from rabbitpox and monkeypox with no serious side effects. Two million doses are stockpiled with the US government should an orthopox-based bioterror attack occur. It is marketed as TPOXX® and given orally. Children weighing more than 13 kg can be given the drug. It is also considered safe in pregnant women. Vaccinia immunoglobulin is obtained from sera of patients vaccinated with smallpox vaccine. It is historically indicated for management of progressive disease following smallpox vaccination, but was also used in the 2003 US outbreak for treatment of monkeypox.

Considering the fact that most cases of monkeypox are self-limiting, no specific antiviral therapy is indicated. Antiviral therapy may be considered in patients with severe and progressive disease, in the severely immunocompromised and in pregnant women [20]. Antivirals have been used anecdotally in the management of MPX in the nonendemic countries. In a recent study, only 5% of the patients received antiviral therapy (2% intravenous/topical cidofovir, 2% tecovirimat, and <1% vaccinia immunoglobulin) [15]. The patient with severe epiglottitis improved rapidly after giving tecovirimat.

Prevention

It has been documented that those individuals who had received smallpox vaccine were better protected against MPX or developed less severe illness as compared to those with no history of smallpox vaccination [22]. Hence, smallpox and modern modifications of smallpox vaccine have been recommended for protection against MPX, though the efficacy is uncertain and needs validation. These vaccines are currently not recommended for mass administration. They are recommended for post-exposure prophylaxis preferably within 4 days/maximally 2 weeks of exposure and for pre-exposure prophylaxis in high-risk individuals including health care workers [25, 27].

The various smallpox vaccines currently available for prevention of monkeypox are listed in Table 1 [1].

The major interventions to prevent an outbreak include: high index of suspicion, early identification, isolation, barrier nursing, and strict infection prevention practices by health care workers [20, 28].

A patient with suspected or confirmed monkeypox infection should be placed in an isolation room; special air handling is not required. The door should be kept closed (if safe to do so). The room should have a dedicated bathroom. Standard precautions should be applied for the patients with suspected monkeypox. Activities that could resuspend dried material from lesions, e.g., use of portable fans, dry dusting, sweeping, or vacuuming should be avoided. Transport and movement of the patient outside of the room should be...
Details
All authors contributed to the review of literature and therapeutics as well as preventive measures. None.

and therapeutics as well as preventive measures are not very available, course of illness and treatment is not well defined, and misconceptions in the public. While it is the disease in the nonendemic countries that has gathered world attention, focus should be on controlling the disease in Africa where most of the deaths continue to occur. The lesson for the future is to not ignore neglected tropical diseases. In the current age of globalization, “no one is safe unless everyone is safe” [29, 30].

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Declarations
Conflict of Interest None.

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