World Applied Sciences Journal 40 (2): 47-53, 2022
ISSN 1818-4952

DOI: 10.5829/idosi.wasj.2022.47.53

Monkeypox: An Overview

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Abstract: Monkeypox virus (MPV) is an orthopoxvirus belonging to the Poxviridae family that is now causing attention all over the world. It has two known viral clades and is indigenous to Central and Western Africa. Natural reservoirs most likely exist in a variety of African rodents and primates. By coming into close contact with diseased animals, zoonotic transmission happens (*e.g.,* slaughtering, scratches, bites). Close contact with infected people (such as through respiratory droplets, skin-on-skin contact, or sexual communication) or fomites can cause human-to-human transmission. Historically, the human MPV disease presents with a skin/mucosal lesion with a diffuse maculopapular to vesiculopustular eruption after a fever prodrome and lymphadenopathy. The febrile prodrome may be missing in the 2022 outbreak, which mostly affects sex partners who are males. Moreover, skin/mucosal lesions might be limited to the anal and genital regions. JYNNEOSTM and ACAM2000® are the available vaccines until now. Antivirals such as brincidofovir tecovirimat, cidofovir and vaccinia immune globulin intravenous are the existing treatments for MPV, albeit the majority of cases will have a self-limited and moderate disease, with sufficient supportive care. Antivirals should be taken into account in severe cases of illness, immunocompromised persons, children, breastfeeding and pregnant women, complicated lesions, as well as when lesions develop close to the eyes, mouth, or genitalia. This short review's goal is to give a brief overview of MPV.

Key words: MPV · Outbreak · Human · Prevention · Treatments

INTRODUCTION

MPV: MPV virus (MPV) is a Poxviridae family member of the Orthopoxvirus genus that is causing international concern. It is a DNA virus related to the smallpox virus. It is endemic to Central and Western Africa and has two viral clades; Congo Basin (Central African) as the more virulent clade and West African as the less virulent clade [1].

The natural reservoirs are almost clearly African rodents and primates. Direct contact with infected animals results in zoonotic transmission (*e.g.,* bites, scratches, slaughtering). Contact with diseased individuals such as skin-on-skin contact, respiratory droplets, sexual contact, or fomites results in human-to-human transmission. From the first time symptoms emerge until the rash has completely cured and a new layer of skin has developed, a person with MPV can transfer it to others [2]. Typically, the human MPV disease manifests as a diffuse maculopapular to vesiculopustular skin or mucosal lesion eruption after a fever prodrome and lymphadenopathy [3, 4].

Epidemiology: In 1958, MPV was discovered in Copenhagen, Denmark during the vesiculopustular skin eruptions outbreak in crab-eating macaques at an animal facility [5]. Another MPV outbreak occurred among monkeys at a research facility in the following years, with a larger outbreak among anteaters and other primates in the Rotterdam Zoo in 1964. Since its first discovery, MPV has shown a proclivity to infect and cause disease in a wide range of mammalian animals from all over the world. This discovery has hampered the identification of the natural host, though African squirrels and/or other rodents are the most likely candidates. MPV can infect animals through a variety of different inoculation routes in experiments. In the 1970s, the children with lymphadenopathy, diffuse vesiculopustular rash and fever constituted the majority of those with the foremost human MPV disease cases, which were found in Central and Western Africa [6]. Mostly in the Congo Basin during the following decades, hundreds to thousands more confirmed human MPV disease cases appeared [7]. Prior to 2022, Central or Western Africa tended to be the only place where human MPV illness was discovered or

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associated with overseas travel or the importation of animals from these regions [4]. However, the UK confirmed numerous human cases of MPV disease in May 2022, despite no clear travel or animal links to these areas. Additional cases were reported in over 20 nonendemic countries by the end of May, indicating rapid human-to-human transmission. By the end of July, approximately 20,000 confirmed human MPV disease cases had been recorded in more than 70 nations on six continents, with more than 5,000 of those cases occurring in the United States [1]. The majority, but not all, of these cases were found to be among men who have sex with men (MSM) and epidemiologic analyses suggested that human-to-human transmission was most likely taking place through close physical contact, skin-on-skin and/or sexual interaction across social networks [8].

Clinical Manifestations: In typical humans MPV illness, a prodrome of fever, malaise, headache, myalgia and/or lymphadenopathy develops four to seventeen days after exposure [3, 4]. This is followed by a maculopapular rash that may be painful or itchy, it transforms into lesions called vesiculopustular. These diseases can affect the oral mucosa, face, trunk and extremities and are often similar in size from stage to stage of progression, well-circumscribed and possibly umbilicated. The disease typically lasts two to four weeks and with low mortality rate. However, the characteristic prodromal symptoms of the current MPV outbreak, which is named the West African clade are frequently absent or manifest only after the rash [8]. The rash associated with this outbreak is reported to start in the genital, oral and anal mucosal areas as well as surrounding skin areas and may not spread to other areas. There have also been reports of severe urethritis, balanitis, proctitis and pharyngitis. Bacteria have also been found to infect the lesions. Patients are said to be infectious once symptoms such as prodromal or rash appear until lesions scab over, fall off and a fresh layer of skin or mucosa forms beneath. These mucosal and skin lesions may resemble acute human immunodeficiency virus (HIV), varicella zoster, syphilis, herpes simplex, or molluscum contagiosum [4].

MPV in Children: Based on the limited data from previous outbreaks, children may be more vulnerable to severe forms of the disease, with possible complications such as sepsis, encephalitis and death [9]. Jezek *et al.* [10] confirmed the clinical features and outcomes of 282 patients with MPV in the Democratic Republic of the Congo from 1980 to 1985; 90% of patients were 15 years old (the youngest being 1 month old). In August 2022, the Florida Department of Health (FDOH) reported a suspected case of MPV in a 2-month-old infant who was admitted to a hospital in Florida with cellulitis and rash [11]. During the 2022 outbreak, 27 MPV confirmed cases have been reported in pediatric patients aged 0-15 years in the United States [11]. Although children may be at a higher risk for developing a severe form of the disease, clinical manifestations in children with MPV have been comparable to those in adults [12].

Test Signs: MPV is a disease that poses surveillance and laboratory capacity challenges for healthcare workers and public health worldwide. MPV, a typically endemic disease, has recently been reported to blow out to non-endemic areas, with an increasing number of cases across North America, Europe and Australia [7, 13-18]. This might be due to the traveling of more infected people, fewer investigation measures in place and more relaxed COVID-19 events. Furthermore, the vaccine for smallpox, which affords approximately 85% protection against the infection MPV, has not been used since 1982. Any available epidemiological data should be used to aid the surveillance process. In the 21 days prior to the onset of symptoms, a number of the initial patients reported traveling abroad, including trips to countries where MPV is not an endemic disease as well as participation in big gatherings and other activities that allowed for close, direct skin-to-skin contact. The recent travel history of a person does not, however, prove that they picked up their infection while abroad. Since late June, an expanding number of confirmed cases have been connected to local society transmission [2].

As previously stated, symptoms and clinical signs are not specific. Due to the numerous conditions that could cause skin rashes, the diagnosis of MPV solely on the basis of clinical manifestations might be a challenge, specifically in cases that have an atypical appearance. Moreover, the clinical manifestations might be atypical more frequently in the 2022 outbreak. Consequently, it is crucial to take into account other likely origins of various skin lesions or a spreading rash. Skin lesions with similar appearances at different stages of development may be caused by a variety of diseases, such as the varicella zoster virus, herpes simplex virus, enterovirus, molluscum contagiosum virus, measles, scabies, syphilis, rickettsia pox, bacterial skin infections, drug allergies, parapoxviruses, or other conditions [19-22].

Clinicians should be on the lookout for patients who present with new representative rash or who reach one of the epidemiologic conditions and have a high clinical skepticism for the MPV. The rash related to MPV is similar

to those seen in herpes, varicella and syphilis patients. There have been reports of patients co-infected with the MPV virus and other infectious agents such as varicella zoster, herpes and syphilis [19, 22-26]. Some countries lack the ability to test. The choice to test must be based on epidemiological and clinical factors, as well as an evaluation of the chance of infection. Anyone who is contacted with clinically and epidemiologically suspected case definition for MPV should be tested [16, 27].

Sampling, Shipment and Storages

Safety Measures: Adequate standard operating procedures (SOPs) should be guaranteed to be used for MPV sample collection, storage and handling. Throughout the sample handling process, personnel of the laboratory should be qualified on how to appropriately use and eliminate personal protective equipment (PPE). Suspected MPV patient samples should be treated as potentially infective material; care should be taken to minimize the danger of infection and all precautions must be taken. It should employ qualified and knowledgeable employees. PPE should be employed with caution and the development of infectious aerosols should be prevented. Vaccination of employees is recommended if available. Healthcare workers, in particular, who are caring for or will be caring for a patient who is diagnosed with MPV should indeed be vaccinated with two doses as normally mandatory. Some sexual health clinic personnel who are evaluating any suspected cases should be included [2]. Quaternary ammonium compounds and freshly made bleach at 0.5% (or 200 ppm) can both be used Pre-exposure vaccination must be prioritized for the staff with high-risk for exposure: personnel estimated to care for MPV cases in high-risk units of infectious disease [2, 28, 29].

Suitable Samples for MPV: Exudate swabs and lesion crusts from the surface and/or skin materials are suitable samples of MPV [19, 28, 30-32]. To obtain enough viral DNA, swabs should be vigorously scrubbed against the lesion. If applicable, swab samples should be collected from multiple locations and lesion types and these samples must be brought dry or on a Viral Transport Medium (VTM) to the laboratory. Crusts, lesions and vesicular fluids shouldn't be delivered all in one tube; however, two lesions of the same type are allowed. False positive or false negative test results can both occur during the MPV diagnosis process. When testing for the MPV, the U.S. Food and Drug Administration (FDA) is encouraging personnel to use the samples collected straight from a lesion's rash or growth using swabs. U.S. FDA is not aware of any clinical evidence using other sample types, like saliva or blood, to test for the MPV. False test findings could come from using samples that were not collected from a lesion [20, 33].

Samples of rectal fluid semen, urine and/or genital tissue might also be collected, depending on the clinic. Although the MPV viremia stage is short and the virus may not be as prevalent as in lesions, a blood sample may support the MPV diagnosis. The biopsy of the macular stage should be performed by professionals with extensive experience [2, 31-33]. The plasma/serum antibody test alone would be insufficient for diagnosing MPV. The presence of IgM in acute infection or the increase in IgG in two different samples taken 21 days apart aids in the diagnosis. Vaccination has an impact on serological test results [31, 34].

Vaccines Against MPV Virus: Vaccination with the smallpox vaccine appears to protect against the MPV virus and might improve the symptoms of infection. The US Strategic National Stockpile (SNS) by now is having three different smallpox vaccines: JYNNEOSTM and ACAM2000® already licensed for smallpox; and another vaccine named Aventis Pasteur Smallpox Vaccine (APSV) is now under investigational new drug (IND) protocol and might be used for smallpox [35, 36].

JYNNEOSTM represents a non-replicating and attenuated orthopoxvirus vaccine that was designed from the modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain) [37]. The U.S. FDA approved this vaccine in September 2019 for preventing both MPV and smallpox diseases in 18 years old adults and older who are at high risk of infection with smallpox or MPV [37]. Smallpox vaccination with vaccinia virus has been shown to be effective against MPV by approximately 85% [38]. In Europe this vaccine is approved for smallpox as IMVANEX®, while the UK has been using this vaccine off-label in response to MPV infections [39].

The ACAM2000® vaccine contains live vaccinia virus as well. The U.S. FDA approved it in August 2007, instead of the orthopoxvirus vaccine Dryvax®, which had been set aside by the producer company. The ACAM2000® is approved for the active vaccination for smallpox disease in people who have been reported to be at high risk of infection. During an outbreak, the CDC maintains an emergency access IND protocol that permits the usage of ACAM2000® for MPV as a non-variola orthopoxvirus infection [37].

Treatments for MPV Virus

Supportive Care: The majority of MPV patients get well without any drugs. Those experiencing gastrointestinal symptoms such as diarrhea or vomiting will need intravenous/oral rehydration to reduce the loss of gastrointestinal fluid [40].

Antiviral Drugs: Numerous antiviral drugs may be effective against MPV infections, though these drugs were approved for the control of smallpox infections using animal models. In humans, several studies to detect the suitable doses of these drugs have been conducted, but the effectiveness of these drugs has not been systematically evaluated [40].

Tecovirimat the antiviral drug, also known as TPOXX or ST-246 was the first to be approved for smallpox treatment in infected infants weighing as a minimum as 3 kg and adults, it is now representing the preferred drug [37]. Double treatment with brincidofovir and tecovirimat may be used in patients who claimed severe symptoms. The tecovirimat drug inhibits the envelope protein VP37 of the virus, which blocks the final steps of the development of virus and its releasing from the infected cell, preventing the virus from spreading to other cells and tissues within the infected host [41]. Although the efficiency of this drug against MPV in humans has not been verified, animal studies have revealed that animals treated with tecovirimat live longer than placebo-treated animals at various disease stages [42, 43]. A safety extensive study that was conducted on human volunteers given the tecovirimat drug with a total number of 359, reported that the side effects outline by the placebo was mostly like the side effects of tecovirimat [42]. Previously, tecovirimat drug were used in combination with vaccinia immune globulin (VIG) in patients having eczema vaccinatum as a complication of the smallpox vaccine [44, 45] and progressive vaccininia [46]. According to the CDC's Emergency Access Investigational New Protocol, the tecovirimat drug could be used to treat MPV as a non-variola orthopoxvirus infection. The protocol also allows children weighing less than 13 kg to mix an oral capsule with liquid or soft food. The Strategic National Stockpile provide tecovirimat in the form of an intravenous vial or an oral capsule [37].

In the United States, brincidofovir has been accepted for smallpox disease treatment since June 2021 [37]. Cidofovir as an oral equivalent of the injectable medication, brincidofovir, might have a better safety profile than cidofovir, including less renal damage [47]. These medications function by inhibiting viral DNA polymerase [48]. The effectiveness of brincidofovir against orthopoxvirus infections has been demonstrated, despite the paucity of studies examining its usage in treating MPV infections in animal models [49, 50]. Although there are few clinical studies on cidofovir's effectiveness against MPV in humans, it has been shown to be effective *in vitro* against deadly MPV virus infections in animals. It is necessary to administer cidofovir together with probenecid treatment and intravenous normal saline. As brincidofovir may result in elevations in serum transaminases and serum bilirubin, liver function tests must be performed both before and during treatment. These treatments are accessible through an IND or EUA [51, 52].

The US FDA has approved the hyperimmune globulin known as Vaccinia Immune Globulin (VIG) to treat specific vaccine-related side effects [52]. These include severe generalized vaccinia, vaccinatum eczema, progressive vaccinia, vaccinia infections in people with skin conditions and vaccinia virus-induced unusual infections except in isolated keratitis cases such as ocular infections [52]. Even though a potential treatment, data on the efficacy of VIG against MPV and smallpox is limited and the use of VIG for MPV or smallpox in humans has not been tested. Because the vaccinia virus vaccination is circumcised in patients having severe T-cell function immunodeficiency, patients with a history of exposure might be given VIG instead [53]. VIG treatment must be performed under an IND application.

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