



Monkeypox Virus Pathophysiological Effects on Human Organ Systems: A review

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Abstract

In view of the increasing incidence of this disease and the potential to cause systemic illness in humans, the emerging zoonotic orthopox virus, monkeypox virus (MPXV), has recently gained worldwide attention. An infection with MPXV has the potential to cause illness in various body systems apart from the skin. The effects of monkeypox infection on the gastrointestinal, neurological, cardiovascular, lymphatic, respiratory, and integumentary systems are discussed in this review. The systemic effects of monkeypox infection, such as fever, lymphadenopathy, respiratory distress, and neurological effects, are due to a combination of pathophysiological mechanisms. The pathophysiological mechanisms include viral multiplication, immune response, and inflammation. Sepsis and secondary infections are the systemic effects of monkeypox infection in immunocompromised individuals. There is an urgent need to address the Mpox virus infection globally with international collaborations in surveillance and studies on rapid response systems to understand the evolution and mutations of the virus.

Keywords: Monkeypox virus, Treatment, Skin, Immune response, Genitourinary Lesions, Circulatory System.

Introduction

Monkey pox, a zoonotic infection, has transformed from a local endemic problem to a serious global public health concern. According to reports from the World Health Organization and the Centers for Disease Control and Prevention, a large outbreak of monkey pox was observed in May 2022, with over 95,000 cases and over 180 deaths in 110

non-endemic countries, confirming a dramatic change in the global epidemiological landscape, highlighting a shift in the virus's mode of transmission and its ability to perpetuate long-term human-to-human infection [1],[2]. This illness is caused by the monkeypox virus, a double-stranded DNA virus, and has genetic relationships with the variola virus, also known as



smallpox, and belongs to a family called Orthopoxvirus and a subfamily called Chordopoxvirinae, a family of Poxviridae [3]. The virus was first identified in 1958 by the Statens Serum Institut in Copenhagen, Denmark, following two outbreaks of a viral infection resembling the pox virus in cynomolgus monkeys. The monkeys had been imported from Singapore to investigate the development of the polio vaccine [4]. Researchers later suggested that grivet monkeys, which are highly susceptible to MPXV and often transported from Africa to Europe and North America, might have served as a source for the virus among the Asian monkey populations during transport [5]. The first recorded incident of human monkeypox was reported in August 1970, in a remote village called Bokenda, located in the Equateur province of the Democratic Republic of Congo (DRC) [6]. The Poxviridae virus family comprises large, enveloped particles containing double-stranded DNA genomes [7]. The genome structure is also complex, varying from 128 to 365 kbp depending on the viral genus (Parapoxvirus and Avipoxvirus, for example), and may contain over 200 different genes [8]. The details regarding the evolution of these viruses are still unclear, although there is a clear indication that these viruses have been around for thousands of years. The genome composition of these viruses is thought to have evolved through the acquisition and loss of genes, primarily through horizontal gene transfer (HGT) [9]. Interestingly, many genes found in poxviruses are not required for replication in cell culture. Instead, they influence how the virus interacts with and evades the host's immune response, which makes them key contributors to viral virulence [10]. Some of these genes, referred to as host-range genes, play an important role in determining which species or types of cells the virus can infect,

giving poxviruses a unique pattern of host specificity and tissue tropism [11].

Pathophysiology:

MPXV gains access to the human body through various paths, including oropharyngeal, nasopharyngeal, and intradermal inoculation [12]. Interestingly, it was also demonstrated that MPXV can potentially be transmitted into the body via sexual intercourse [13]. Human-to-human transmission may take place through contact with an infected ulcerated skin lesion or mucosa, or respiratory droplets [14]. In addition, touching virus-contaminated objects such as garments, tableware, and furniture is also a concern [15].

Once the virus enters the body, it begins to replicate at the point of inoculation, and from there, it gradually moves to the nearby lymph nodes as it starts to spread further [16]. After an incubation period of 1 to 3 weeks, several symptoms may manifest, such as fever, chills, malaise, headache, sore throat, backache, dyspnea, and lymph node enlargement, to name only a few [17]. The infected individual becomes infectious between one and three days after the onset of fever and the appearance of lymphadenopathy, which is when the rash typically occurs, usually beginning on the face before becoming generalized [18] (Fig 1). The primary routes of human infection (oral, oropharyngeal, nasopharyngeal, and intradermal), as well as the subsequent systemic spread to local lymph nodes, are depicted in the diagram. Additionally, it illustrates the progression from prodromal symptoms (fever and lymphadenopathy) to the emergence of widespread skin lesions following the incubation period [19].

The crucial roles that the COG (specifically COG4/COG7) and GARP (VPS52/VPS54) complexes play in viral morphogenesis are highlighted by the three different stages of the replication process (early, intermediate,

and late). These complexes facilitate maturation by wrapping intracellular enveloped viruses (IEVs) in a Golgi-derived membrane. This process leads to the formation of cell-associated enveloped

viruses (CEVs), which are subsequently released as infectious extracellular enveloped viruses (EEVs) via actin-mediated expulsion [20], [21].

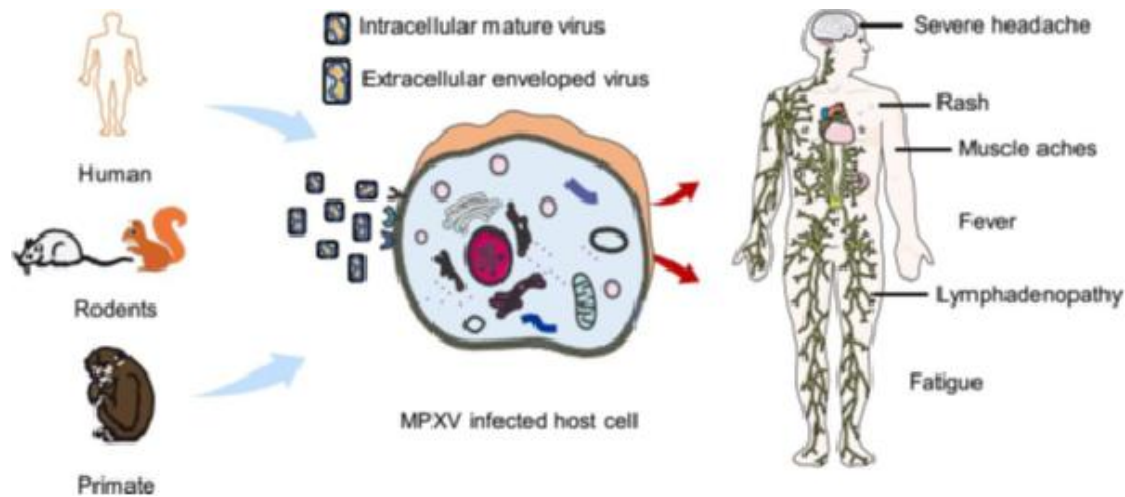


Fig. 1: A schematic showing how the monkeypox virus (MPXV) is spread and how it infects people, along with the symptoms of monkeypox (MPX) [17].

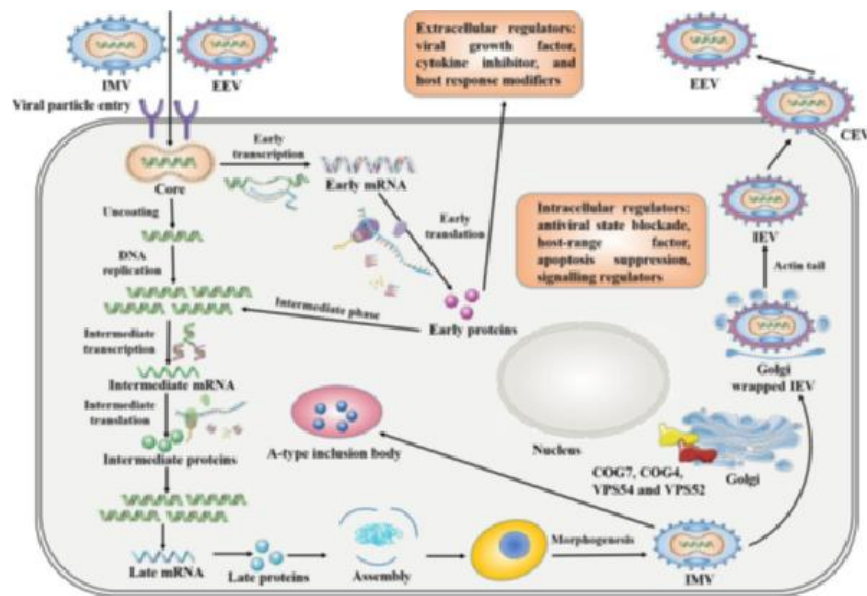


Fig. 2: illustrates how MPXV infects target host cells [20].

Epidemiology of MPXV

Between 1980 and 1985, in Zaire (at the time of the first human recognition), a total of 282 cases were recorded. The patients' ages ranged from 1 month to 69 years, with 90% of the victims being under the age of

15. No mortality was reported among vaccinated subjects, while the mean fatality rate for unvaccinated patients was 11%, reaching higher levels among children (15%) [19] (Table 1).

Table 1: Epidemiological information regarding reported MPXV cases Classified by country and gender.

Gender/Age (year)	Number/Ratio of cases	Year	Country	Reference
Gender: Male	2.5 male: 1 female 99%	2017	Nigeria	[22]
	,About 7500 cases, male is 99% of cases 579/582 (99.5%) confirmed cases are male.	2022	U.S.	[23], [24]
		2022	Ontario, Canada	
Gender: Female	Uncommon 3/582 (0.5%) are female.	2022	U.S.	[25]
		2022	Ontario, Canada	
Age: Those under 15 years old	Uncommon	2022	U.S.	[24]
Age: 21–40	Male is 2.5 times larger than female.	2017	Nigeria	[25]
Age: 26–40	Constitute the largest percentage of cases.	2022	U.S.	[24]
Age: < 20 – 74 years) with mean = 36.4 years	582	2022	Ontario, Canada	[23]
Age: under than 40–50	Recently, this generation is now vulnerable to monkeypox due to a smallpox vaccination stop due to smallpox eradication in the world	2022	U.S.	[26]
Age: above 60	Uncommon	2022	U.S.	[24]
Age & Gender are not reported	3–5	2022	Saudi Arabia	[24]

Genitourinary Lesions Due to Monkeypox

Monkeypox virus (MPXV), a member of the Orthopoxvirus genus, can replicate in a wide range of cultured mammalian cells. These include kidney-derived cell lines such as pig embryonic kidney, baby hamster kidney

(BHK), human kidney, and rabbit kidney cells [27]. Thus, kidney tropism in humans is also conceivable. To date, no specific host-cell receptors have been identified to explain how poxviruses bind and subsequently enter cells. Crucially, while a wide variety of cell lineages may be infected, only a small percentage eventually permit the completion

of the full replication cycle [28]. In currently known cases, only a small number of individuals received empirical antiviral therapy, which primarily involved the use of cidofovir. [29] , Cidofovir is a well-documented nephrotoxic compound that induces apoptosis within proximal tubular cells, frequently resulting in clinical manifestations such as Fanconi syndrome and acute kidney injury (AKI) .In a randomized clinical trial involving individuals with human immunodeficiency virus (HIV) and cytomegalovirus-related retinitis, nearly 40% of the subjects treated with cidofovir exhibited proteinuria [30]. Notably, the deleterious effects of antivirals lacking demonstrated efficacy against the monkeypox virus may outweigh their theoretical advantages (Fig. 3) [31].

The immune response to monkeypox virus:

Research has demonstrated that acute monkeypox virus (MPXV) infections are associated with various immunological perturbations, including natural killer (NK) cell dysfunction, lymphopenia, elevated antibody titers, and increased monocyte and granulocyte counts. In addition, these infections are associated with immune evasion, cytokine storms, suppression of the host complement pathway, and antibody-dependent enhancement phenomena. A more detailed overview of these phenomena can be seen in (Fig. 4) [17].

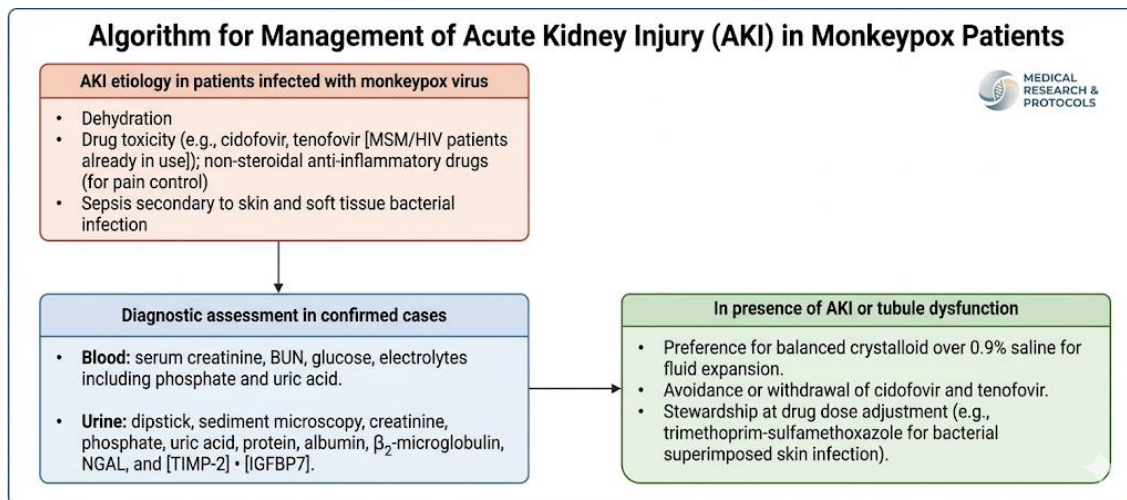


Fig. 3: Overview of the causes, diagnosis, and management of acute kidney injury (AKI) in patients infected with the monkeypox virus, highlighting the risks of drug-induced nephrotoxicity, sepsis, and dehydration [6].

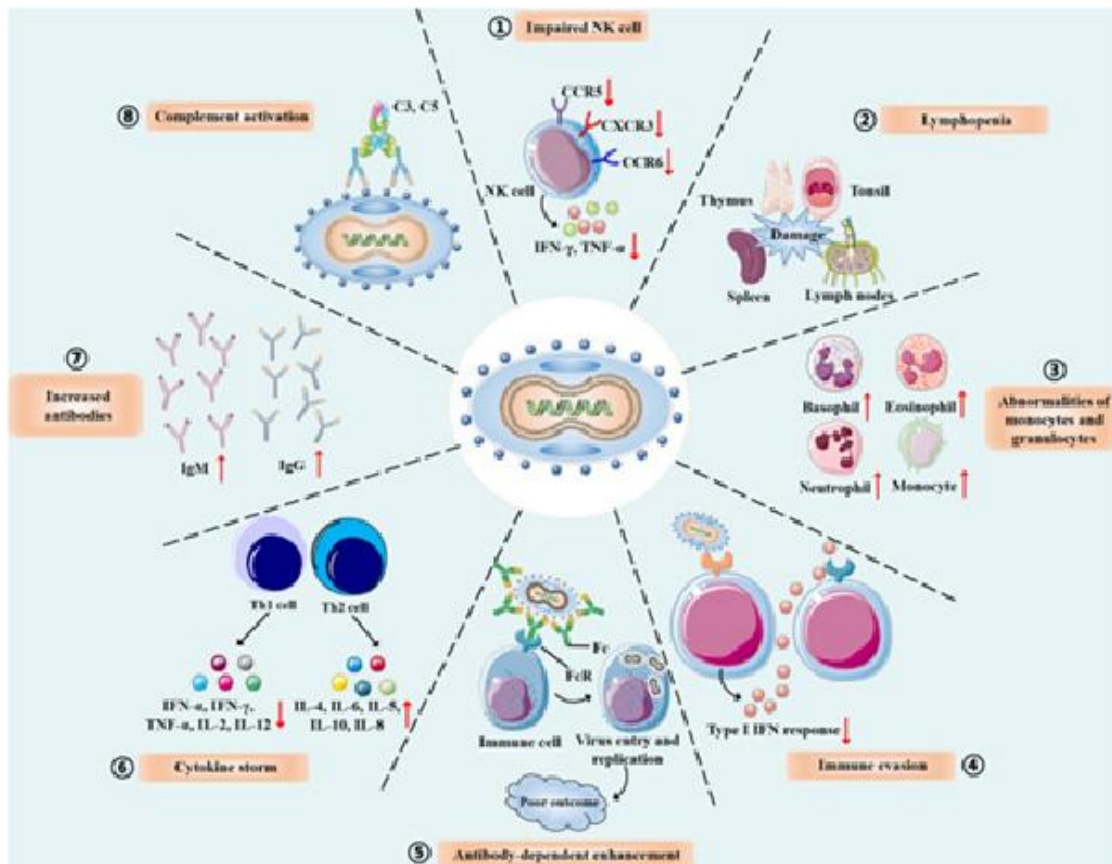


Fig. 4: Overview of the immunopathogenesis of MPXV, emphasizing its capacity to induce a Th2-dominant cytokine storm while suppressing innate immunity and Th1 responses. The diagram also illustrates the virus's involvement in complement system dysfunction, immune organ damage, and antibody-dependent enhancement (ADE).

Effect of monkeypox virus on the circulatory system

MPXV most commonly infects skin and mucous membranes, and it is due to this that skin lesion manifestation is common. However, emerging research has indicated that this virus may have the ability to infect endothelial cells, thereby traversing and affecting other parts of the body, including the cardiovascular system, as it is most likely that this system will be affected due to its integral role within the body and its potential interaction with other body parts. It is essential that more is understood about its effects on the cardiovascular system [32].

Some research has proposed potential mechanisms for smallpox vaccine-related myopericarditis. It is suggested that the virus could impact the myocardium either through direct viral invasion or via an immune-mediated response. This hypothesis is consistent with those findings of a Th1-dominant cytokine response associated with myocarditis following smallpox vaccination [33]. Since orthopoxviruses are closely related to vaccinia virus, the smallpox vaccine, it is even possible that Mpxv be linked to myocarditis as well [34]. Based on the analogy with smallpox vaccination, it could be assumed that the Mpxv virus can show a tropism for cardiac muscle tissue, or perhaps trigger an immune-mediated damage

of the heart. Further investigation on the pathophysiological chains linking Mpox infection and heart conditions is needed since it may influence patient prognosis [35]

The effect of monkeypox virus on the nervous system

As of October 2024, Unlike herpesviruses, flaviviruses, retroviruses, or enteroviruses, poxviruses have not been considered classical neurotropic viruses [36]. The ability of orthopoxviruses to infect and seriously harm the neurological system is becoming

more widely acknowledged (Table 2).20–22 Concerns about the effects of poxviruses on the central and peripheral neurological systems are raised by new information, especially from the 2022 mpox an outbreak that highlights the viruses' ability to affect the nervous system and cause neurological complications [37]. With a major focus on MPXV, we address the neurotropic and neurovirulent properties of orthopoxviruses in this review. Along with the neuropathogenic mechanisms behind CNS and PNS disorders, we also go over the clinical and demographic characteristics linked to neurological symptoms (Fig. 5).

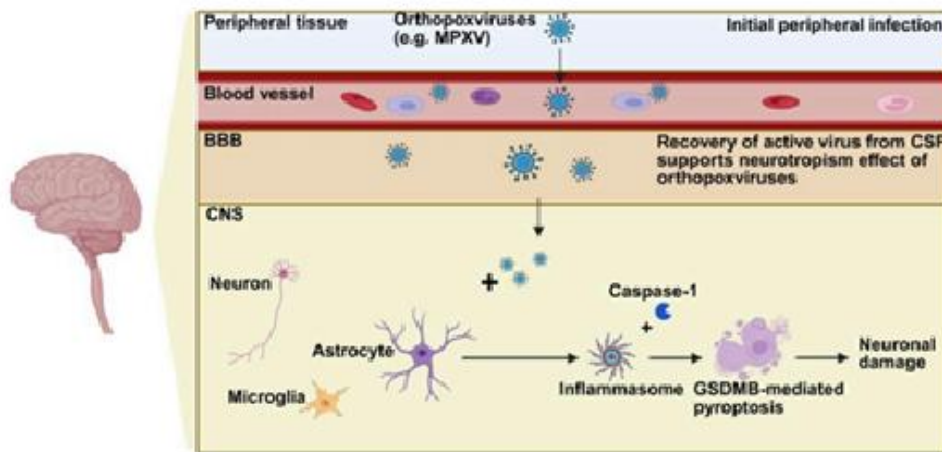


Fig. 5: demonstrates how the monkeypox virus invades the nervous system, emphasizing the blood-brain barrier's movement and astrocyte infection. It demonstrates how the monkeypox virus causes GSDMB proliferation and inflammatory cell death, which in turn causes neurological damage [38].

The effect of monkeypox virus on the digestive system

The monkeypox virus causes certain clinical symptoms and impacts the digestive system and organs. Patients experience issues with their digestive systems, including nausea,

vomiting, diarrhea, dehydration, and malnutrition [39]. It has been noted that nausea and vomiting are less common in adults and more common in children, particularly [40]. While liver and other intra-abdominal organ involvement is uncommon, it can result in major consequences [41]. Some studies have found granulomatous alterations and infections in the peritoneum, intestines, and

stomach. According to certain research, there can be consequences for the liver and liver tissue [42].

Early in May 2022, cases of monkeypox - now often called Mpox - began spreading worldwide, drawing strong attention from doctors. Because it affects the whole body, you might expect more studies on gut-related signs or impacts on the liver. Yet evidence looking into these areas is still surprisingly limited. One up-to-date analysis that gathered and assessed multiple studies [38]. One early study took a close look at stomach and gut issues in people with Mpox. It turned out many showed signs like belly pain or changes in how their liver worked [22]. Appetite fading showed up more than any other gut issue during monkeypox infections. After that came feelings of nausea, then sickness, belly discomfort, or loose bowels. Rectal inflammation, which was uncommon before, was what made the 2022 wave stand out. These days, it's one of the obvious indicators that keeps appearing [43].

Effects on Skin and Related Structures

Skin changes are one of the main ways Mpox (monkeypox) presents itself. Flat spots typically start the progression, which progresses to elevated bumps, fluid-filled blisters, and finally pus-filled sores. Before scabs eventually form, these lesions frequently develop an indentation in the middle. The disease did, however, manifest differently during the 2022 outbreak than it had previously. The most common locations for sores were inside the mouth or around the genitalia, and these skin lesions frequently

preceded systemic symptoms like fever or body aches [44].

Respiratory System Effects

Transmission of mpox through large airborne droplets can affect the respiratory tract. Some of the earliest symptoms of mpox in the respiratory tract are a sore throat and a persistent cough; however, the course of the clinical illness can be quite unpredictable. In severe cases, mpox infection of the respiratory tract may lead to pneumonitis (inflammation of lung tissue) or to a secondary bacterial infection. Patients with weakened immune systems are at higher risk for the development of respiratory complications that can progress to respiratory failure and require intensive care and mechanical support [44].

Lymphatic System and Swollen Lymph Nodes

Mpox can be distinguished by its lymph node swelling, meaning that it can be distinguished from diseases such as smallpox and chickenpox. Lymphatic swelling may appear in an area such as in the glands under the jaw, in the neck or in the armpit, and is often present before the characteristic rash has developed. The enlargement of these lymph nodes reflects the body's immune response to the virus as it begins to spread from the initial site of entry [45].

Diagnosis

It is impossible to confirm a Mpox diagnosis based solely on a patient's signs and symptoms since they cannot be differentiated from illnesses brought on by other poxvirus family members [46]. Laboratory testing plays a key

role in identifying Mpox early. Current methods include PCR to detect viral DNA, immunohistochemistry, culturing rash samples, examining the virus under an electron microscope, and blood tests to measure antibodies against the virus [47]. The World Health Organization prefers PCR as the method of choice for detecting Mpox. Swabbing fluid from sores works best - think blisters, open wounds, or scabs. Though blood tests detecting IgM and IgG may help confirm past infection, results sometimes get muddled when reacting to similar poxviruses or earlier smallpox shots [48].

Next generation gene scanning is now being implemented in some laboratories today to help differentiate between strain one and strain two viruses. The need for precise identification of each virus is critical to being able to track changes in the virus over time. Recognizing that there are differences between strains helps determine how to respond to a global outbreak. It does not change the method of treatment for the virus; it makes the complete picture sharper. Clarity comes not from speed alone but from accuracy over time [49].

Therapy

As with other Orthopoxvirus infections, the primary goals of the best treatment for Mpox infections are symptom relief, minimizing complications, and preventing infection sequelae [50]. Orthopoxvirus can be treated with two antiviral medications: Cidofovir, which is delivered intravenously, and Brincidofovir, which

is administered orally [51]. Two antivirals are effective against Orthopoxvirus: Cidofovir, an intravenous agent and Brincidofovir given by mouth, the anticamptothecin tecovirimat, an antiviral that inhibits intracellular virus release and is used to treat small pox, was approved for the treatment of potentially lethal infections caused by variola (small pox) virus via FDA's animal rule. In 2022, tecovirimat was approved by the European Medical Association (EMA) for treatment of Mpox [48]. VP37 is an ancestral viral protein that the Mpox virus uses to get out of infected cells and infect new ones [52]. Tecovirimat blocks the VP37 viral protein, stopping the Mpox virus from exiting infected cells and spreading to others [53].

Vaccination

The smallpox vaccine does not provide full protection, but it can lower the risk of infection with monkeypox. but it can help reduce the risk of getting monkeypox, it's important to steer clear of animals you suspect might be infected and follow good hygiene practices, such as washing your hands often and staying away from people who are sick. Those measures are critical to reducing the likelihood of catching or transmitting the virus [54] (see Table 1).

Table 2 compares several vaccinations now in use in various nations according to their type, recommended dosage, target population, and mode of administration [55], [56], [57].

Number	Vaccine	Type	Route of administration	Recommended number of doses
1	ACAM2000	Live attenuated (2nd generation)	Percutaneously	single dose
2	JYNNEOSTM/MVA-BN)The Ankara strain of the Vaccinia virus) with third-generation MPX antigens(Under the skin	Two dosages in a 28-day period
3	LC-16	Third-generation live attenuated	Through the skin	Two dosages in a 28-day period

Table 2: A comparison of various vaccines utilized for the protection of Monkeypox (MPXV).

Smallpox vaccines were developed in three main stages. At first, they were made by putting the virus on a calf’s skin and then collecting it from the calf’s lymph [58]. At the moment, these vaccines aren’t approved for use in large-scale vaccination programs. The newer, second-generation smallpox vaccines are made using modern methods and grown in cell cultures, which makes them safer. The main orthopoxvirus vaccines available are LC16, JYNNEOS, and ACAM2000 [59]. In 2015, the FDA approved ACAM2000 for protection against smallpox and monkeypox in the U.S. For the next few years, from 2015 to 2019, it was the only monkeypox vaccine available in the country [57],[60].

Discussion

Monkeypox virus, or MPXV, is a serious issue that has become a growing concern for world health organizations and figures worldwide because, despite its appearance as a rash on one’s skin, this virus has numerous effects on other parts of one's body. Additionally, serious illness is more common in some communities due to this virus. The virus multiplies primarily in the body’s mucous membranes and skin, but its ability to travel through blood and lymph pathways means that other parts of the body can be affected as well. Such is why most of these patients can develop general symptoms such as fever, tiredness, and lymph nodes that are swollen. Additionally, respiratory problems can occur especially if it is able to travel as a body fluid, resulting in serious respiratory issues for these patients. Equally, digestive

problems may be experienced, especially diarrhea, vomiting, and dehydration, making it more difficult for these patients to deal with their condition as well.

Sometimes the brain can be affected when someone gets a monkeypox infection, leading to intense headaches, swelling in the brain, or fits. Heart problems like inflammation of heart muscle or lining around it show up now and then, especially if the body's defenses are weak or vaccination is missing. People who are already susceptible might suffer even worse, and body-wide chaos from immune reactions and failures in vital organs has also been seen

People who are immune-compromised are more susceptible to serious monkeypox infection. This includes individuals suffering from HIV, those who have had an organ transplant, and pregnant women. When a person has late-stage HIV, especially when CD4 levels are below 200 per microliter, the virus can disseminate throughout the body. Instead of mild symptoms, they may experience deep, necrotic sores on the skin. Their risk of death increases significantly when compared to those whose immune system functions normally [61]. In the same way, when people undergo organ transplants and are on long-term immunosuppressive therapy, they are more likely to shed viruses over time. To make things even more serious, they are more likely to acquire bacterial infections later on. If an expectant mother is infected with the monkeypox virus, things get more serious. The mother and child are at risk of something different. The child is at risk of birth defects when the mother is infected. The mother is at risk of death before delivery. Labour in neonates also affects psychological development [48].

The involvement of monkeypox in the infection of multiple organ systems also points to the need to have good surveillance, as well as conducting relevant research and cooperation among nations. Good scientific

and medical research and good prevention are necessary to manage existing cases, and to plan for prevention of future outbreaks.

Limitations

Monkeypox is a disease that has no available antiviral medications, so it is very difficult to evaluate how to manage and treat monkeypox. Because monkeypox can be transmitted from animal to human (and therefore is of significant concern), it is essential for all levels of government to coordinate with each other in supporting research and development of either a vaccine or an antiviral drug that will effectively treat this destructive disease [62]. Due to the potential of monkeypox being spread throughout the world and to every area of the world, it is urgent that monkeypox research and development be prioritized [46].

Conclusion

Mpox is now beyond solely being a skin disease to having an extensive effect on the body. As well as causing lesions on the skin, the virus can attack key organs of the body, including the heart, brain, kidneys and gastrointestinal tract. Studies have documented that heart function may be affected; neurological pathways may become affected in abnormal ways; kidney function and the functionality of the GI tract may demonstrate significant alterations as a result of the virus. A major reason for the multi-organ effect of the virus is due to the rampant production of virus and the virus's sophisticated strategies to maintain an infection. The important viral products that allow for undermining of the immune system are the COG and GARP proteins. Although PCR tests continue to be relied upon as the most reliable method of diagnosing mpox, patients suffering from severe mpox or

complications from their infection (especially those who may be immunosuppressed) require more than just the knowledge that they are infected; they require treatment such as antiviral medications (e.g., tecovirimatan, as well as other novel antiviral treatments). Additionally, the use of third-generation vaccines as a preventative and control strategy has become an essential prevention and control measure when used appropriately. Therefore, contemporary mpox management places an emphasis on acting quickly and accurately rather than relying solely upon rapid diagnostics. Monkeypox's future trajectory is contingent upon detailed scientific monitoring of the disease. By accurately observing symptoms in patients and also conducting analyses of genetics and labs, scientists can begin to see the various patterns of disease that may exist. It is important to create a comprehensive disease solution/analysis from both clinical data and genetic data; when one piece of data is missing, the picture may not be complete. Continued successes within both areas of patient care and genetics will give us viable solutions for future issues associated with monkeypox.

Conflict of Interest

Authors declare there is no conflict of interest.

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الآثار الفيزيولوجية المرضية لفيروس جدري القروود على أجهزة الجسم البشري: مراجعة

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الخلاصة:

(، وهو MPXV نظراً لانتشاره المتزايد وقدرته على التسبب بأمراض جهازية لدى البشر، فقد حظي فيروس جدري القروود) على العديد من MPXV فيروس جدري حيواني المنشأ ناشئ، باهتمام عالمي واسع النطاق مؤخراً. يمكن أن تؤثر عدوى أجهزة الجسم بالإضافة إلى الأعراض الجلدية المعتادة، مما يؤدي إلى طيف واسع من النتائج السريرية. تتناول هذه المراجعة آثار جدري القروود على الجهاز الهضمي، والجهاز العصبي، وجهاز القلب والأوعية الدموية، والجهاز اللمفاوي، والجهاز التنفسي، والجهاز الجلدي. وتنتج الأعراض الجهازية، كالحمى وتضخم الغدد اللمفاوية وضيق التنفس والمضاعفات العصبية، عن مجموعة من الآليات الفيزيولوجية المرضية التي تشمل تكاثر الفيروس، وتنشيط الجهاز المناعي، والاستجابات الالتهابية. قد تؤدي الحالات الشديدة، وخاصة لدى الأشخاص الذين يعانون من ضعف المناعة، إلى تسمم الدم، أو عدوى ثانوية، أو فشل متعدد الأعضاء. ثمة حاجة ماسة إلى تعاون دولي في مجال المراقبة، ودراسات أنظمة الاستجابة السريعة لفهم تطور الفيروس وظفراته، مما سيسهم بشكل كبير في تصميم اللقاحات واستراتيجيات العلاج لمكافحة فيروس جدري القروود.

الكلمات المفتاحية: فيروس جدري القروود، العلاج، الاستجابة المناعية، آفات الجهاز البولي التناسلي، الجهاز الدوري.