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Review

Another Epidemic in the Shadow of Covid 19 Pandemic: A Review of Monkeypox

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Abstract

While humanity has not been able to end the fight against the COVID-19 pandemic, newly reported cases of monkeypox have caused unease. The current review sheds light on the transmission routes, pathogenesis, clinical presentation, treatment, and prevention of the disease in this early stage of the ongoing monkeypox epidemic.

Keywords: Monkeypox, epidemic, outbreak, orthopoxvirus

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While humanity is still struggling with the COVID-19 pandemic, on May 7, 2022, a case of monkeypox was reported to the World Health Organization. The patient had a history of travel from the UK to Nigeria and then back to the UK.[1-3]

Monkeypox is a zoonotic disease commonly occurring in Central and Western Africa. The disease is caused by the monkeypox virus (MPV), a virus belonging to the genus *Orthopoxvirus*, which also includes variola, the causative agent of smallpox. The symptoms of monkeypox are similar to those of smallpox.[2,3] MPV has two major clades: West African and Congo basin clades. West African clade is less virulent and has a mortality rate of <1%. The current epidemic is thought to be caused by Western African clade.

The disease historically made sporadic endemics mostly in the Democratic Republic of Congo (DRC) and Nigeria and was extremely rare outside of Africa.[1,3] However, in the current epidemic we are facing, there are nearly a hundred confirmed monkeypox cases in the USA, UK, and many other European countries as of May 21, 2022.

The purpose of this review is to outline the future implications of the ongoing monkeypox epidemic and to shed light on the course of the epidemic by reviewing the current scientific knowledge on the disease.

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Transmission Route and Infectivity

MPV is known to be transmitted from animals to humans. Animals that mainly harbor the virus include rodents (rats, squirrels, and dormice) and various species of monkeys.

However, a human-to-human transmission that took place both in and out of Africa has also been documented. MPV may be transmitted through direct contact with skin lesions of infected animals or humans, respiratory exposure of droplets from infected humans, or bushmeat.[4,5]

In the ongoing epidemic, it is observed that the disease is more common in males who have sex with males.[5,6] Although this is not sufficient to categorize monkeypox under sexually transmitted diseases, there is evidence that the disease can be transmitted by close contact.

In a mathematical modeling study, the authors reported the R0 value of monkeypox to be between 1.10 and 2.40 in countries where exposure to *Orthopoxvirus* species is negligible, and this value suggests that an epidemic of monkeypox is imminent in these settings in case of imported human or animal cases.[4-6]

Virology

Monkeypox belongs to the *Orthopoxvirus* genus in the Poxviridae family. It is one of the *Orthopoxvirus* species that infect humans, along with the variola virus, which was exterminated by vaccinations derived from the vaccinia virus. Poxviruses are DNA viruses that contain a joint nucleoprotein antigen with a length of 220–450 nm and a width of 140–260 nm. Virions are large and have a brick-shaped appearance. It is a virus that replicates in the host cytoplasm with its double-stranded DNA with a double-layered cell membrane. Virions contain enzymes, involving the RNA polymerase system, for the primary transcription of structural and viral genes.[7–9] Their proteins are found in the M (mulberry) form with 10-nm long protrusions on the surface and less commonly in the C form containing 20–25-nm thick electron-dense capsules. The virus' receptor is yet to be discovered. Nonetheless, after fusing, the half-moon-shaped membrane structures transform into a circular shape, surround the nucleoprotein structures, and create intracellular immature virions.[7,10] They become intracellular enveloped virions by synthesizing viral proteins in the Golgi apparatus.[9,10] Eventually, they exit the cell as mature virions. The process can be expressed as the fusion of the viral structure, shedding, spreading of viral contents into the cell, and initiation of transcription of early viral proteins.[7-10]

Pathogenesis

Infection is a race between the replication process and the activation of the host's immunological defenses. The viral characteristics and the level of the host response determine the severity of the disease. The large size and complexity of *Orthopoxviruses* enable the host to easily generate the immune response. Smaller viruses can breach the host's defenses by passing through gaps or rapidly replicating, whereas larger viruses such as *Orthopoxviruses* need a more comprehensive strategy to survive within the host.[11–13] A set of molecules encoded by virulence genes act as modulators by being directed against components of the host's immune response. These modulatory proteins can be divided into two groups according to their intracellular and extracellular actions. Virotransducer proteins act within the cell, interfering with the cell's response to infection, including oxidative burst and apoptotic pathways. Another group of proteins that acts within the cell is virostealth protein, which reduces the likelihood of detection by the immune system through downregulation of immune recognition molecules such as major histocompatibility complex class I and CD4. Viral proteins, also called viromimic proteins, which act extracellularly, function to modulate the immune response. They can be classified as viroreceptors and virokines. Viroreceptors are secreted or cell surface glycoproteins that bind host cytokines and chemokines competitively, interfering with their actions. Virokines form viral mimics of host cytokines, chemokines, and growth factors, which are effective both in subverting host responses that are detrimental to virus survival and in promoting responses appropriate for viral replication and spread.[13–15]

Although the skin rash has been linked to MPVs, it can quickly lead to mortality in susceptible individuals infected with virulent strains that produce an extreme immune response. In addition to the tissue-damaging cytopathic effects of Orthopoxviruses, overproduction of endogenous mediators and soluble cytokines can lead to sepsis and septic shock, as in COVID-19. The viral components produced to control the inflammatory behavior in the host response and the exaggerated immune response of the host can trigger mortality during the disease phase.

Clinical Presentation

MPV has an incubation period of 4–21 days. Initial symptoms of monkeypox include nonspecific ones such as fever, headache, muscle aches, backache, lymphadenopathy, chills, and exhaustion. Clinical presentation of monkeypox resembles smallpox. Besides that, MPV infection can be distinguished from smallpox with the early enlargement of lymph nodes (maxillary, cervical, and inguinal), usually occurring synchronously with the onset of fever. The enlarged lymph nodes can be 1–4 cm in diameter and may be tender, firm, and painful. Following fever and lymphadenopathy, rashes appear 1–3 days later. Rashes are peripheral and si-

multaneous, but they can cover the whole body with the severity of the disease. The disease resolves with the desquamation of rashes 4 weeks after the initial symptoms.[16,17]

There are several complications that the patients may suffer from. The rashes may occur in the oral cavity which may deteriorate nutrition. Patients are prone to secondary bacterial infections of the skin lesions. Corneal infection may lead to scarring and consequent loss of vision. Bronchopneumonia may be another complication, particularly in patients coinfected with influenza. Also, exaggerated immune responses may result in sepsis and septic shock.[16–18]

The diagnosis can be made via immunological methods such as ELISA, polymerase chain reaction, electron microscopy, and phenotypic and clinical presentation of disease in the absence of laboratory confirmation. Though, The specificity of diagnosis on clinical evaluation alone is low.[18,19]

Treatment

Currently, there are no specific treatments for monkeypox disease. However, experience with smallpox suggests that the vaccinia vaccine, cidofovir, tecovirimat, and vaccinia immune globulin (VIG) may have a use in monkeypox treatment.

Although the efficiency of traditional smallpox immunization has been extensively demonstrated when used as a preventive measure, and post-exposure vaccination is part of the WHO eradication strategy, little is known regarding its efficacy when used after MPV exposure. Nevertheless, considering the efficacy of the vaccinia vaccine on MPV, one may think that post-exposure prophylaxis with the vaccinia vaccine may work in preventing in MPV infection as well. Though this has to be confirmed in clinical studies.[20,21]

Tecovirimat was found to have specific efficacy on several *Orthopoxviruses* (variola, vaccinia, cowpox, ectromelia, rabbitpox, and monkeypox).[21,22] Although there is no data on the effectiveness of Tecovirimat in human cases of monkeypox, it is shown to be effective in treating Orthopoxvirus-induced disease in animal studies.[20-22]

Since 1996, cidofovir has been used to treat cytomegalovirus (CMV) retinitis in AIDS patients. It is effective against almost all DNA viruses, including herpes, adeno, polyoma, papilloma, and poxviruses. Vaccinia, variola (smallpox), cowpox, monkeypox, camelpox, molluscum contagiosum, and orf have all been shown to be sensitive to the inhibitory effects of cidofovir. Brincidofovir is a lipid conjugation of cidofovir, a nucleotide analog. There is no evidence that Cidofovir and Brincidofovir are effective in treating human instances of monkeypox. In vitro and animal investigations, however, both have demonstrated effectiveness against poxviruses.[22-24]

VIG was previously used to treat individuals who had been exposed to smallpox. Patients who were at high risk of experiencing complications following smallpox immunization were additionally given VIG. As a result, post-exposure VIG treatment may regain importance as a therapeutic technique in systemic Orthopoxvirus infections caused by variola or MPVs.[23,25]

Possible Reasons of Re-emergence of Disease

The reemergence of infectious diseases involves many interrelated factors. Global accessibility continues to increase with international travel and trade. The increase in economic, political, and cultural relations makes human–human and animal–human interactions more evident. These interactions allow for accidental and deliberate sharing of microbial agents. Outbreaks of three monkeypox cases were also reported in the UK between May 25, 2021, and June 15, 2021.[26,27] The first case was found to have traveled from Nigeria on May 8, 2021. This statement can be given as an example showing how important the facilitation of global transportation is in the transmission of the disease. Interhuman transmission of the MPV, although limited, causes epidemics, particularly in the home and healthcare settings. But current evidence suggests that without repeated zoonotic introductions, human infections will not eventually emerge. Further spread of animal–human relations poses the risk of transmission from animals to humans.[26,27] Therefore, stopping the transmission of viruses from animals to humans can be considered one of the most important steps in the fight against this disease.

It should be kept in mind that the use of the smallpox vaccine may affect the recurrence of the disease. Monkeypox, which was first described in DRC in 1970, is known to have emerged after the cessation of vaccination after the eradication of smallpox. In the following years, after the eradication of smallpox with vaccination, its existence in the same geography with different epidemiological patterns and field results aroused suspicion.[28] The termination of the administration of the vaccine may pave the way for the increase of susceptible individuals. Again, failure to provide vaccination to susceptible individuals in geographical settlements where HIV infection is common can be counted among the factors that may cause the disease to reemerge. Reviewing the vaccination program, identifying susceptible individuals, and ensuring vaccination can be of great importance. Although rare cases of monkeypox have been reported outside of African countries, little effort has been made to develop a specific vaccine to eradicate the disease.[2] The reemergence of infectious diseases during an ongoing pandemic is worrying.

The world population is increasing. With the advancement of technology, earlier detection of malignancies, effective treatment opportunities of chronic diseases with the developing pharmaceutical industry, the use of therapeutic and prophylactic drugs used in the prevention of thromboembolic events, and the widespread use of invasive procedures (such as angiography laboratories) contribute to the prolongation of the average life span. The increase in the world population together with the increasing average life expectancy means an increase in the population of sensitive people. The termination of vaccination, the increasing population, the extended life expectancy, and the increase in global relations as a result of easier transportation can be counted among the possibilities that may cause the re-emergence of monkeypox disease.

Preventive measures

According to CDC, there are several ways to prevent infection with MPV:

- Avoiding contact with animals that are capable of harboring the virus or any materials that have been in contact with a sick animal.
- Avoiding animals that are sick or dead where the disease is endemic.
- Taking isolation measures for infected patients.
- Washing hands or using alcohol-based hand sanitizers after contact with infected animals or humans.
- Using personal protective equipment such as masks and gloves while caring for the infected.[29]

Raising public awareness and educational interventions may also be beneficial in reducing the transmission of the virus.

Consideration of Re-use of Vaccinia Vaccination en Masse

It is reported that the vaccinia vaccine, which is used to eradicate smallpox, is also effective in eradicating monkeypox. As both smallpox and MPV share the same genus, past studies indicated that the vaccinia vaccine may provide approximately 85% protection and reduce disease severity. [30] Considering the fast progression of the monkeypox epidemic, we may need to reuse it en masse to protect masses from being infected.

Conclusion

This monkeypox epidemic and the ongoing COVID-19 pandemic have shown that zoonotic diseases are serious threats to humankind. In the increasingly globalizing world, any pathogen emerging from anywhere can be a danger for all countries and all humanity in no time. COVID-19 pandemic sadly taught us that awareness and preparedness are two keywords to tackle these dire situations. Governments should adapt and learn to act simultaneously and be swift in implementing control measures without any hesitation.

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