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COMPREHENSIVE LITERATURE REVIEW OF MONKEYPOX: PATHOPHYSIOLOGY, EPIDEMIOLOGY AND CURRENT TREATMENT

Abhijeet Singh*, Sanjoti, Ankush, Dr. Neeraj Bhandari, Ankush Uppal and Ashish Kumar

Student of B. Pharmacy, School of Pharmacy, Arni University Kathgarh, Indora, Distt. Kangra H.P Pin Code 176-401.

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***Corresponding Author**
Abhijeet Singh
Student of B. Pharmacy, School of Pharmacy, Arni University Kathgarh, Indora, Distt. Kangra H.P Pin Code 176-401.

INTRODUCTION

Significant efforts are being made to rid the population of the disease in high-prevalence geographic areas.[1] Variola is regarded as a disease that can spread from person to person; no other known reservoir of the smallpox virus has been found. Recently, a very comparable pox condition known as "monkeypox" was discovered in monkeys, raising questions about the clinical and epidemiological connections between these two illnesses. In terms of its clinical manifestation, monkeypox is comparable to smallpox or the development of widespread vaccinia in humans.

The origin of monkeypox raises a number of significant problems about its epizootiology. Was it an unintentional spread of the variola virus in 14 captive monkeys that a human companion was harboring? Is it a form of the variola virus that was formerly adapted to simians and is currently enzootic in some species? Regarding the vaccinia virus.

Lastly, the question of whether monkeypox could be brought on by another, as yet unidentified, member of the variolavaccinia complex is addressed. Furthermore, as human cases of natural monkeypox virus (MPV) infection have been documented, epidemiologic consequences must unavoidably be considered.[2,3]

It has been fourteen years since MPV was recognized. This illness in a nonhuman monkey has shown itself to be a very good model from a nosographic perspective for a study of the varied features of infection and immunity of a poxvirus infection. Theaccessible data on (i) MPV, (ii) the disease's evolution in simians, and (iii) to reevaluate the epidemiological potential in relation to an extrahuman reservoir of anotther poxvirus capable of causing human illness.

Pathogenesis

MPXV shares similarities with VARV and the Vaccinia virus (VACV) in terms of pathogenesis and mode of action.[4] MPXV likely infects a variety of mammalian cells, similar to other poxviruses, without requiring particular host receptors or chemicals for cell entry and replication.[5] Through interactions between MPXV surface proteins and main attachment receptors (glycosaminoglycans) on the host cell membrane, the extracellular enveloped virus (EEV) virions bind and enter the host cell, initiating the infection process.[6] Three proteins have been identified as viral entry proteins that may help MPXV enter host cells through receptor binding and membrane fusion, although there is still a paucity of information on particular MPXV proteins implicated in host cell entrance and the receptors on host cells. The first is protein L1, a protein found in virus membranes that most likely attaches itself to entrance receptors on host cells. Although research on VACV indicates that this envelope protein interacts to the cell surface, the precise functions of protein L1 during MPXV entrance are unknown.

Through the entry/fusion complex (EFC) and is required for merging the virus membrane to the host cell membrane during viral penetration,[7-9] E8L is another MPXV cell surface-binding protein that is suggested to bind to host cell surface chondroi tin sulphate proteoglycans (CSPG) and mediate adsorption of intracellular mature virus (IMV) virions to cells.[10] The MPXV envelope protein H3L has also been studied in in-vitro and in-vivo on VARV, indicating important roles for this protein in virus adsorption to cell surface heparan sulphate and IMV morphogenesis.[11] Despite the variability in surface glycoproteins and the number of wrapping mem branes between the IMV and EEV virions[12], IMVs that exit infected cells through budding can also penetrate the cellular membrane and infect other host cells, but less efficiently than EEV.[13]

Epidemiology

Only a few isolated cases of human MPX sickness were documented in a number of African nations during the past century. In the 1970s, a nine-month-old boy in the Democratic Republic of the Congo was found to be the first human to contract MPX.[14] Subsequently, 11 other African nations—Cameroon, the Democratic Republic of the Congo, Nigeria, Benin, the Central African Republic, Gabon, South Sudan, Côte d'Ivoire, Sierra Leone, and Liberia—reported isolated instances.[15] Between February 1996 and February 1997, there was a significant MPX outbreak in the DRC that included 511 affected cases.[16]

There was an MPX outbreak in the US in 2003, with 47 confirmed or suspected cases. sick prairie dogs housed in a pet distribution facility with other mammals, including the anticipated first host, African rodents from Ghana, were believed to have exposed the sick patients to the virus.[17] At the end of 2018, Nigeria saw 116 confirmed cases with a 6.7% mortality rate and 280 suspected cases, the majority of which were in individuals under 40, according to Petersen et al.[18]

The DRC reported a 20-fold increase in cases between 1981–1986 (7.2/100,000 population) and 2006–2007 (144.2/100,000 population), as well as a 5-fold increase from 2001 (0.64/100,000 population) to 2012 (3.11/100,000 population).[19] The disease's incidence has dramatically increased. The number of cases of human MPX disease has increased since the 1970s, according to Bunge et al.[20], who extracted data from 28 peer-reviewed published articles and 15 grey literature reports. The median age of infected cases increased from 4 years old in the 1970s to 21 years old between 2010 and 2019.

MPX was seen in children and adolescents in endemic areas during earlier outbreaks, and the clinical picture and intensity of symptoms were thought to be identical to those in adults. But according to a new WHO report, severe MPX cases are more common in children and are correlated with the level of viral exposure. Additionally, poorer MPX outcomes may be linked to the patient's health status, the type of problems, and underlying immunological deficits. Because immunization against SPX, which may provide protection against MPX, stopped when SPX was eradicated in the 1980s, adults born after that time are more vulnerable. Furthermore, although it was previously thought that MPX infected men and women equally, the current multi-country outbreak has shown a large number of MPX cases among men who have sex with other men (MSM). Gay, bisexual, and transgender individuals are at heightened risk of contracting MPX since, according to the CDC,

Although there have been reports of MPX coinfection with other blood-borne pathogens and sexually transmitted diseases (STDs) [198], patients with HIV are the most concerned because HIV infection is thought to be a risk factor for MPX during the current outbreak.[21-22]

A poor prognosis, prolonged duration of MPX signs, delayed cure of self-limiting MPX infection, additional comorbidities, and complex treatments are all significantly correlated with an inadequate immune response in situations of advanced or uncontrolled HIV infection.[23]

Laboratory diagnosis

Clinical signs are insufficiently precise to provide a conclusive diagnosis, despite the fact that prompt diagnosis is essential to ending an outbreak. Prior to the development of real-time PCR, a serological test for MPXV-specific antibodies was employed in MPXV-endemic regions with limited resources.[24] As a result, the necessity for diagnostic instruments has emerged. It is recommended that specimens be extracted from crusts, vesicular lesions, or skin exudate and stored cold in a dry, sterile tube. Due to its excellent sensitivity and precision, real-time PCR tests are currently the recommended laboratory technique for detecting MPXV DNA from extracted nucleic acid.[25] Viral isolation from nasopharyngeal and oropharyngeal secretions can confirm the diagnosis.[26]

Skin biopsies can be taken from the vesiculopustular rash or the intact lesion roof. For serologic testing to identify the particular immunoglobulin M and G (IgM and IgG) of MPX within 5 and 8 days, respectively, specific sera are needed. This kind of testing indicates an immune response after vaccination or exposure to other orthopoxviruses, even though it also provides proof of viral exposure.[27] Creating new methods that are more sensitive to immune responses may improve the diagnosis. Large, well-equipped labs are necessary for several diagnostic techniques, but many nations—particularly those with the highest illness burdens—cannot provide these resources. As a result, point-of-care diagnostics that require less training are required for basic labs.

Current treatment and prevention protocol

According to the CDC, receiving an SPX vaccination up to two weeks after being exposed to MPX could lessen symptoms but not prevent sickness during the 2003 MPX outbreak in the US.[28] Nevertheless, neither the general population nor sick individuals can receive the SPX

vaccination. This is explained by worries about administering a live VACV, its expense, and the unidentified side effects in patients with impaired immune systems.[29]

Low-immune patients are particularly vulnerable to severe vaccination-related side effects, such as pneumonia, cardio-related problems, cryptococcal meningitis, and progressive VACV, an uncommon side effect that can cause tissue and skin damage and be lethal.[30-33] ACAM2000 and Imvamune, the second and third generations of SPX vaccines, have been developed.[34] Similar to those documented with the first-generation vaccine[35], and its safety in HIV patients is unknown. According to CDC guidelines from 2015, those with HIV and those with a CD4 cell count between 50 and 199cells/mm3 who were exposed to SPX should take Imvamune, while those with a CD4 cell count greater than 200 cells/mm3 should take ACAM2000. ACAM2000 provides more viral suppression than Imvamune, according to analytical tests.

For MPX, there isn't a single approved treatment. The only ways to manage secondary bacterial infections are to treat them, lessen their symptoms, and provide supportive care. Nevertheless, two medications, CMX001 and ST-246, were created to treat SPX. The FDA has approved ST-246 (tecovirimat) for SPX and it has demonstrated effectiveness against MPX.[36] According to Berhanu et al.[261], ST 246 either by itself or in combination with ACAM2000 was more effective than ACAM2000 alone following MPX exposure. In a study examining the overlapping effects of ST-246 and ACAM2000, the humoral response was decreased but the vaccine's effectiveness remained mostly unchanged. Therefore, it is not recommended to administer ST-246 and ACAM2000 at the same time.[37]

Potential therapeutics

Oral inhibitors of orthopoxvirus infections, including SRI 21950 (a 4′-thio derivative of iodo deoxyuri. Another high-activity substance that needs to be administered parenterally is HPMPO-DAPy.[38]

All three VARV strains and the other orthopoxviruses were inhibited from replicating at pharmacologically feasible doses by CDV, cyclic HPMPC (cHPMPC), HPMPA, ribavirin, tiazofurin, carbocyclic 3-deazaadenosine, 3-deazane platonic A, and DFBA (1-(2,4-difluorobenzyloxy)adenosine perchlorate), a derivative of adenosine N1 oxide. The antiviral effects of bis-POM-PMEA and methisazone, two other drugs, were less potent. Research on the susceptibility of 35 VARV and other orthopoxvirus strains to a subset of the three most

potent substances—ribavirin, cHPMPC, and CDV—to investigate potential inherent treatment resistance in VARV isolates derived fromindicate that almost all isolates show comparable sensitivity across various time periods and geographical locations.[39] Clinical usage of CDV ((S)-1-(3-hydroxy-2-phosphonyl methoxypropyl) cytosine, HPMPC) in AIDS patients with cytomegalovirus (CMV) retinitis has been authorized since 1996. CDV works especially well against all DNA viruses. The poxviruses include VACV, VARV, CPXV, MPX, camelpox (CMPV), molluscum contagiosum, and orf (sheep pox) are susceptible to CDV's inhibitory actions.[40] According to these results, CDV may be helpful in treating and temporarily preventing infections caused by SPX and related poxviruses.[41,43]

Vaccines

Most nations stopped routinely administering SPX vaccinations as a result of the WHO-managed and certified SPX eradication 40 years ago. It is currently estimated that more than 70% of people on the planet are not immune to SPX and similar orthopoxviruses like MPX. Despite an outbreak in the UK in 2018, there was minimal push to develop SPX vaccines that would offer cross-protection against MPX.[44] An informal, ad hoc group of interested experts met in London's Chatham House in June 2019 to talk about these issues, examine the data that was available, and determine the research needs pertaining to MPX. It was decided that a deeper comprehension of the orthopoxviruses' genomic evolution and evolving epidemiology, the value of in-field genomic diagnostics, and the most effective disease control measures, like immunization,[45]

CONCLUSSAION

The source of infection and all routes of transmission should be taken into account in epidemiological research aimed at controlling the current MPX outbreak. In order to control the current outbreak, new methods for the clinical treatment and prevention of MPX are provided by the current therapeutic regimens and vaccines that have been demonstrated to be effective against SPX. The FDA-approved anti-SPX medications (CMX001 and ST-246) have demonstrated efficacy against MPX, despite the fact that management of MPX infection is still restricted to treating secondary bacterial infections, symptom reduction, and supportive care. Testing therapies with demonstrated antiviral properties against VARV or other poxviruses in this emergency scenario could hasten the development of anti-MPXV medications. Additionally, the world ought to reverse the challenges encountered during infectious disease outbreaks.

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