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Review Article

Pathology Section

Monkeypox Pathogenesis, Transmission, Preventive Measures and Treatment Modalities

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ABSTRACT

Monkeypox is a disease transmitted through animals but can also spread from human to human. The causative agent is monkeypox virus which is a ds-DNA virus. Monkeypox virus belongs to the orthopox genus of the poxviridae family. Other members of this family are the variola virus and the vaccinia virus. This virus was first discovered in 1958. In 1970, when various types of research were going on to eradicate smallpox, the first case of smallpox in humans was reported in the Democratic Republic of Congo. Both smallpox and monkeypox share the same clinical features. Other symptoms are adenopathy and papular rashes. Monkeypox can spread through various modes of transmission. The most common mode is direct contact with contagious animals or contagious humans. Disease progression can be limited by spreading awareness, among the people about the factors responsible for transmission, clinical manifestations, and preventive methodologies.

Keywords: Poxvirus, Smallpox, Viraemia, Zoonotic disease

INTRODUCTION

Viruses belonging to the Poxviridae family are enveloped and possess ds-DNA [1]. Transmission of the monkeypox virus is infrequent in humans are the common hosts of poxviruses are non human primates, rodent, and rabbit [2]. According to taxonomical classification, the Poxviridae family is again classified into two families: Chorodopoxvirinae and Entomopoxvirinae [3]. The Chorodopoxvirinae family is further categorised into 18 genera. Smallpox virus and monkeypox virus have similar clinical presentations [4]. World Health Organisation (WHO) announced the global monkeypox outburst an international emergency, more than 16,000 patients over more than 70 countries had been infected with the virus. Only five patients had died, and no one outside of Central and West Africa, where the disease is endemic. This shows a mortality in the current global outburst of approximately 0.03%.

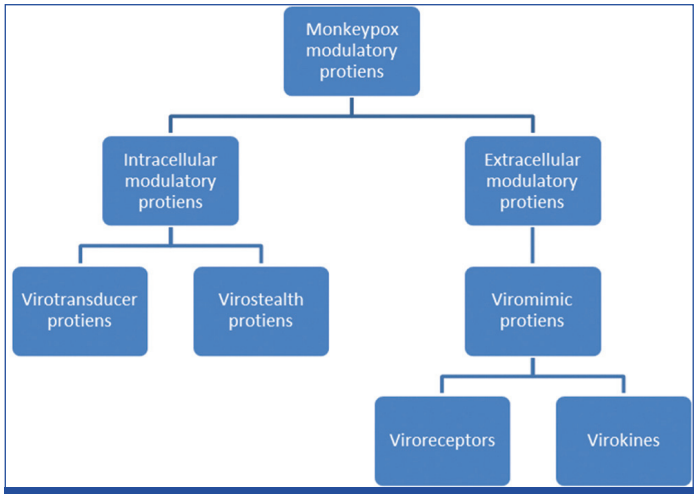
Yet, as per the reports of WHO, mortality rate of monkeypox is approximately 3-6% years [5]. In the early 1970's, monkeypox was noticed only in hosts other than humans [6]. Patients belonged to 42 states, of over five WHO regions, from 1st January 2022. Overall, diagnosed cases were 2103 from 1st January to 15th June 2022, which included one fatal case and one infected case. From May 2022, maximum patients were seen [7].

Pathogenesis of Monkeypox

The Central African (Congo Basin) clade and the West African clade are two definite genetic clades of the monkeypox virus. The Congo Basin clade is more virulent and is responsible for greater severity [8]. During the 2003 US outburst, a higher rate of fatality, morbidity, viraemia, and human-to-human transmission was related to the Congo Basin clade of Monkeypox virus [6]. Genomic comparison between Central and West African strains resulted in a set of genes that may be comprised in categorising clade virulence. Central African Monkeypox prevents T-cell stimulation, which inhibits secretion of cytokines of inflammation in human cells deriving from the individuals infected earlier with monkeypox [8]. Hammarlund E et al., observed that in the presence of fewer monkeypox viruses, the immune response which was T-cell mediated was reduced by 75%. This indicates that host T-cell responses are decreased by a regulator that is produced by monkeypox [9].

The monkeypox virus inhibitor of complement enzyme is not present in West African strains. This enzyme contributes to viral virulence and also regulates the host's immune system [10]. This strain decreases the host reactions, by inducing cell death in the host [8]. Some research says that Central African monkeypox silences the gene transcription which is involved in the immunity of the host [11]. Poxviruses are ds-DNA viruses that multiply in the cytoplasm of cells of vertebrates [12]. Usually, DNA viruses undergo replication, and genome expression takes place in the nucleus, but this doesn't happen in Poxviruses [13]. Poxviruses mostly depend on proteins coded by viruses. They help the viruses to multiply in the cytoplasm [14]. The centre of the genome possess genes which perform functions, such as viral transcription, on the other end those found at the terminal end are responsible for virus-host interactions [15]. A total of 150 genes are encoded by the poxviruses, out of which, 50 are seen in sequenced members of the family, and 90 are common within the subfamily of chordopoxviruses [16]. Most of the viral conserved genes are related to their functions and form the centre of the genome [12].

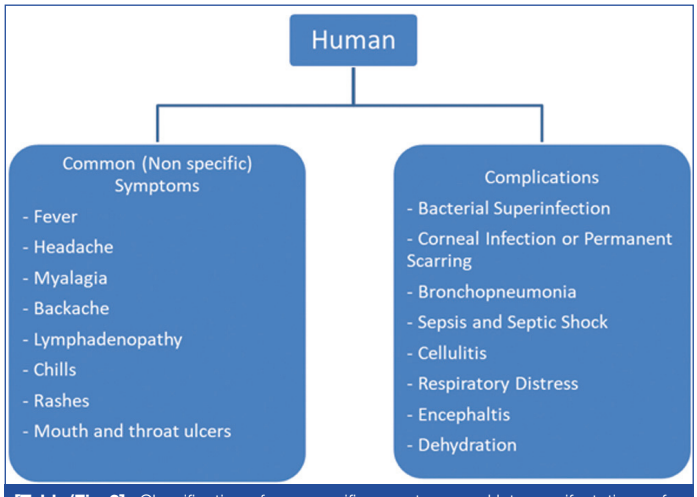
The proteins responsible for regulatory actions against the host's immune system can be divided in two classes based on whether they function inside the cell or outside the cell as mentioned in [Table/Fig-1]. Proteins which are present inside the cell are virotransducer proteins and virostealth proteins. The former play an important role as it interferes with the cell's response to the infection [17,18], while the latter decrease the possibility of identification of the viral particle by the host's immune system [12]. [Table/Fig-1] shows two different categories of viromimic proteins. These two proteins play a major role in regulating the response of the immune system. The viroreceptors found as glycoproteins on the cell membrane competitively bind to cytokines and chemokine of the host [17,18]. As a result, virokines mimic cytokines, chemokines, and growth factors of the host. These proteins decrease the host reaction that, interferes with the survival of viruses and also promotes signals for replication of viruses [4]. These regulatory proteins function simultaneously to destroy the host's immune response to facilitate the multiplication of viruses.



[Table/Fig-1]: Regulatory proteins produced by monkeypox.

Transmission

Monkeypox can spread through various modes of transmission. The most common mode is direct contact with contagious animals or contagious humans [Table/Fig-1]. Most human infections are due to close contact with contagious animals [7]. Symptoms and late manifestations are shown in [Table/Fig-2] [19]. Transmission from animal to human can be through close contact. Viruses shed in faeces can be another source of infection [20]. Some areas of Africa have scarce resources and infrastructure due to which people sleep outside in open areas or stay near forests, where infectious animals are commonly found [19]. Food scarcity in certain regions can also lead to people with no option, but to hunt and cook small animals, which make them more vulnerable to monkeypox infection. Human-to-human transmission mostly occurs due to prolonged contact of respiratory droplets or direct contact, with lesions of the infected individual [21]. Other sources of contamination are sharing the same beds, living in the same rooms or sharing the same dishes for eating food, and sharing the same household. Other modes of transmission can be close contact with infected articles and direct contact with lesions of an affected patient. Both monkeypox and smallpox share same infectious pathway, which begins with exposure to the respiratory droplets of the susceptible host. The later virus multiplies at the point of entry.



[Table/Fig-2]: Classification of non specific symptoms and late manifestations of monkeypox.

Clinical Manifestations

After viral replication is completed, the virus proliferates to surrounding lymph nodes. During secondary viraemia, the virus reaches the distant lymph node and organs through blood. This complete course is the incubation period, which usually lasts for 7-14 days. No clinical manifestations are seen during the incubation period and hence this period is non infectious [22]. The manifestations of monkeypox can be seen during the prodromal phase. During the prodromal stage, the person is highly contagious. This is because of manifestations like mucocutaneous lesions and enlargement of lymph nodes. The common non specific manifestations are shown in [Table/Fig-2]. These symptoms start to appear 1-2 weeks after an individual has contracted monkeypox [23]. During the prodromal stage, common manifestations that activate the immune system appear like pyrexia, myalgia, enlargement of lymph nodes, etc. Early triggering of the immune system will lead to lymphadenopathy of various sites such as maxillary, cervical, and inguinal along with the beginning of fever. In recent cases, Harris E stated that for few patients, the symptoms of the prodromal stage can be mild or even go unnoticed, indicating that such patients might be unaware of the infection till the rashes appear [24]. In common situations, the temperature decreases on day 1 or upto 3 days after the beginning of rashes. The rashes first appear on the face and then appear centrifugally all over the body [7]. The lesions can be observed in the mouth and these lesions can lead to difficulty in eating and drinking for the patient. These skin lesions lead to excess perturbation of the skin and this can be an opportunity for a secondary infection to occur such complications have been noted in 20% of unvaccinated monkeypox patients [25]. A distinct presentation of rashes is seen in infected patients.

The classic observation seen in monkeypox infection is a disseminated vesiculopapular rash [26]. This rash goes through many stages before entering the desquamation stage. This is the stage where scabs begin to peel off. All these lesions manifest first as enanthem, macule, and papule and then as vesicle and pustule [27]. All the above lesions tend to become crusted within 2-4 weeks [23]. Lesions first appear on the tongue and mouth, then on the skin. These lesions are called enantham. The individual is labelled as non infectious, once the crusted lesions are peeled off. This process is known as desquamation. In some individuals, scars persist once the scab is peeled off. Few cases often manifest as areas of excessive pigmentation and less pigmentation, where the rashes are highly concentrated [28]. In some primates, it has been observed that the severity of the lesion increases as the pustule formation occurs along with rapid ulcer formation, necrosis, and hyperplasia of the interstitium [23]. Further, oedema can be prominently seen at the margins of the area of necrosis. The appearance of inflammation and necrosis indicates that preventive measures are needed to avoid secondary bacterial infections and skin infections [26].

Infected individuals suffer from severe dehydration which occurs due to Gastrointestinal (GIT) manifestations like vomiting and diarrhoea that arise by the 2nd week of infection. The throat and mouth ulcers cause complications with the maintenance of nutrition, furthering possibilities of dehydration in the cases [27]. Vaccinated individuals have fewer complications related to a monkeypox infection as compared to unvaccinated individuals [8]. Because of cross-immunity, people who received vaccination against smallpox in the early 1970's are having fewer chances to develop complications related to monkeypox virus infection. Due to extremely increased immune responses, septic shock and sepsis may also occur [26]. Monkeypox virus infection is usually self-limiting although long-term complications are barely seen. Lobular pneumonia is a late manifestation of monkeypox infection. It is generally found in people that, are also infected with the influenza virus. Lobular pneumonia and severe inflammation can limit the intake of air and decreases the ability of food and fluid intake in the patient [26].

Preventive Measures

A two-fold approach is required for the anticipation. The primary aim must be, to quickly cure the ones who are infected and facilitate care after the exposure to reduce the emergence of infection. The second aim will be to make vaccines accessible. The initial step toward preventing the dispersal is to increase awareness among people and increased surveillance of present cases [29,30]. The information gained from the COVID-19 pandemic can be utilised as certain evidence-based precautionary methods are lacking [31]. From coronavirus pandemic, we learned that prior diagnosis, and isolation of infectious patients, are necessary for a community to be aware to decrease the spread of viral endemics and pandemics [32]. To prevent discrimination, we need to minimise or avoid stigmatisation and optimise disease response. Educational campaigning about the transmission and spread of the disease will aid in minimising the stigma among the common people [33].

Treatment

Monkeypox virus requires several weeks for recovery, as it is a self-limited disease that doesn't require any clinical assistance. However, some patients may require to be hospitalised and may require additional care due to unavoidable symptoms. Anti-viral drug therapy is advised for those patients who are at high-risk of getting infected. Treatment of monkeypox involves the administration of multiple antiviral drugs [34,35]. Tecovirimat is a drug of choice, for many patients among all the available antivirals. Combined treatment of tecovirimat and cidofovir may also be beneficial in patients with severe infections [27].

Tecovirimat: Both oral and intravenously (i.v.) forms of Tecovirimat are available. VP37 Protein present in *Orthopoxovirus* is inhibited by this medication, therefore, the interactivity between the virus and the host cell is blocked. This results in the prohibition of the virus and prevents the host cell from infection. The i.v. dose of tecovirimat depends on the functions of the kidney and the weight of the patient; the duration of treatment is 14 days. There is no contraindication when the drug is administered orally [27]. Tecovirimat is considered to be the first-line treatment in pregnant and lactating females. The dosage used in the study of animals was 23 times greater than the dosage used in humans, yet it didn't show any particular effect on the animal foetus [27].

Cidofovir: Studies in animals demonstrated that Cidofovir is effective against monkeypox [36]. Severe acute kidney failure can occur in high doses of Cidofovir [37]. Patients that are to be given Cidofovir should also be given saline intravenously for rehydrating the patient and probenecid orally [38]. Based on studies, it is indicated that this drug can cause cancer and developmental malformations. The drug has the risk of developing neutropenia; hence, while taking this drug the neutrophil count of a patient must be monitored. There is a threat of liver impairment along with pancreatitis and metabolic acidosis. This drug is contraindicated in pregnant females, as it can cause developmental malformations in the foetus. Cidofovir, brincidofovir should be avoided in lactating females due to its severe adverse effects [26].

CONCLUSION(S)

Monkeypox can be transmitted through various modes of transmission. The most common mode is direct contact with contagious animals or contagious humans. Monkeypox virus is a self-limiting disease which requires some weeks for recovery. Individuals suffer from dehydration, throat and mouth ulcers. Disease progression can be limited by spreading awareness among the people about the factors responsible for transmission, clinical manifestations, and preventive methodologies.

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