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Monkeypox and its global relevance

A varíola dos macacos e sua relevância global

La viruela del mono y su relevancia global

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Abstract
Objective: This study aimed to carry out a literature review to describe the clinical characteristics of Monkeypox, explain its means of transmission, and favor its prevention. *Methodology*: Searches using descriptors in PUBMED Central, BVS/BIREME, Web of Science, Scielo, The Cochrane Library, Google Scholar, and books on the subject, classified as gray literature. *Results*: During the review process on the therapeutic options available for the treatment and prevention of the disease, it can be concluded that the population's access to efficient health has become essential, so that there is effective control of this disease, through vaccination, prevention programs, and information to the population about the means of transmission.
Keywords: Monkeypox; Poxvirus; Virus; Vaccinia; Disease.

Resumo
Objetivo: O objetivo desse estudo foi realizar uma revisão de literatura para descrever as características clínicas da Monkeypox, explicar os meios de transmissão e favorecer sua prevenção. *Metodologia*: As buscas com o uso de descritores na PUBMED Central, BVS/BIREME, Web of Science, Scielo, The Cochrane Library, Google Acadêmico

e livros sobre o assunto, classificados como literatura cinza. *Resultados*: Durante o processo de revisão sobre as opções terapêuticas disponíveis para o tratamento e prevenção da doença, chegamos à conclusão de que o acesso da população à saúde eficiente tornou-se imprescindível, para que haja o controle efetivo dessa doença, por meio de vacina, programas de prevenção e esclarecimento da população sobre os meios de transmissão.
Palavras-chave: Varíola dos macacos; Poxvírus; Vírus; Vacina; Doença.

Resumen
Objetivo: El objetivo de este estudio fue realizar una revisión bibliográfica para describir las características clínicas de la viruela del mono, explicar las vías de transmisión y favorecer su prevención. *Metodología*: Búsquedas utilizando descriptores en PUBMED Central, BVS/BIREME, Web of Science, Scielo, The Cochrane Library, Google Scholar y libros sobre el tema, clasificados como literatura gris. *Resultados*: Durante el proceso de revisión sobre las opciones terapéuticas disponibles para el tratamiento y prevención de la enfermedad, se llegó a la conclusión de que el acceso de la población a una salud eficiente se ha vuelto fundamental, para que exista un control efectivo de esta enfermedad, a través de la prevención vacunal, programas y aclaración a la población sobre los medios de transmisión.
Palabras clave: Viruela del simio; Poxvirus; Virus; Vacuna; Enfermedad.

1. Introduction

Monkeypox is an infectious disease caused by the zoonotic Monkeypox virus of the Orthopoxvirus family, the same family as Smallpox, but with less transmissibility and clinically less serious. Its main symptoms are fever, myalgia, fatigue, headache, back pain, and asthenia (WHO 2022).

Transmission occurs through contact with body fluids, respiratory droplets, contaminated materials, and sexual contact. Having as a risk group the immunosuppressed, because due to their immune system infection they tend to develop the most severe form of the disease, being the first death in Brazil. Children aged 5 years or less are included in this risk group, as they do not have a well-developed immune system, and pregnant women due to their low immunity due to the pregnancy process, in addition to the risk for the fetus to acquire a congenital disease (WHO 2022).

Reports on Monkeypox are not recent, and the first cases in humans date back to 1970, having been identified as endemic in African countries, more specifically in the Democratic Republic of Congo and the Central African Republic (Li et al., 2010). Beforehand, however, in 1958 there were already reports about the disease, which until then only affected small mammals. Currently, the disease is classified as a pandemic with cases of infections in at least 44 countries.

To this degree, the objective of this study was to carry out a literature review to describe the disease, explain the means of transmission and favor its prevention.

2. Methodology

For the accomplishment of this research, online searches were carried out by searching the database available from BVS/BIREME and PUBMED Central. Other portals such as Web of Science, Science Direct, Periodic Portal from CAPES, as well as The Cochrane Library and PROSPERO were also used. For general knowledge concerning the social-economical situation of the African countries, online searches were accomplished to relate the transmission rate of Monkeypox to the health problems detected there.

3. Results

3.1 Disease description

The analysis and description of diseases are the basis for a well-founded diagnosis, capable of clarifying the type of disease we are facing. In this context, Monkeypox fits as a zoonosis and has two different lineages: the Central African lineage and the West African lineage, however, a historical comparison presented in the work of (Patel et al., 2022) indicates that the

strain from Central Africa has greater virulence. Caused by the contagious viral agent Orthopoxvirus, which results in a disease very similar to smallpox in humans. In this way, the work of (Bunge et al., 2022) states that smallpox in humans was initially diagnosed in 1970 in the Democratic Republic of Congo (DRC), and has spread to other regions of Africa. To clarify the disease, the authors carried out a systematic review of the literature that explained how Monkeypox evolved, with emphasis on the number of confirmed, probable, or possible cases. Age at diagnosis, mortality and geographical distribution of the disease was also taken as a basis. The authors concluded that the number of cases of the disease in humans has been increasing since the 1970s, with the most dramatic increases occurring in the Congo. The median age at presentation has increased from 4 (1970) to 21 years (2010-2019). There was an overall fatality rate of 8.7%, with a significant difference between clades - Central Africa 10.6% (95% CI: 8.4% - 13.3%) versus West Africa 3.6% (95%: 1.7% - 6.8%). Finally, the authors concluded that the appearance of outbreaks outside Africa highlights the global relevance of the disease.

Descriptions of the biology of Monkeypox infection were provided by the work of (Alakunle et al., 2020). They claim that after 39 years with no case reported in Nigeria, transmission to other parts of the world occurred in 2018 and 2019, respectively. They report recombination, genetic gains, and losses, in the evolution of Monkeypox, explain the role of signaling in the infection, and review current therapeutic options available for the treatment and prevention of the disease. Furthermore, they performed a genome-wide phylogenetic analysis and showed that Monkeypox isolates from the recent 2017 outbreak in Nigeria were monophyletic, with the isolate transmitted to Israel from Nigeria, but did not share the most recent common ancestor with the isolates. Obtained from previous outbreaks, in 1971 and 1978, respectively. These data indicate that the virus, following the normal course of viral infections in the world, undergoes repeated mutations to survive. Knowing the history behind the disease is essential for the comprehension of its development, and it is of extreme interest to study its symptomatology. The most common symptoms detected in those infected with Monkeypox are prodrome, headache, myalgia, lymphadenopathy, skin eruptions, and genital or perianal lesions (Angelo et al., 2022).

3.2 Transmission

Monkeypox has traditionally been transmitted through contact with blood, body fluids, or skin rashes from infected people or animals. It is also possible to get infected by contaminated objects and by breathing in droplets during a contagious phase (the most symptomatic and dangerous).

Cases related to the occurrence of the MPX virus have been reported since May 13, 2022, with the majority being reported in non-endemic regions in countries in Europe, North America, and Australia (Multi-Country Monkeypox Outbreak in Non-Endemic Countries).

After many thoughts about the etiopathogenesis of the virus, many questions arise about the viral variants and their lethal power. In this way, it was discovered that there are two variants of MPXV, corresponding to the two specific locations of Africa: West Africa and Central Africa, with a presumed lethality rate of less than 4%, but with a higher prevalence in patients with HIV, and that of the Congo Basin, with a much higher lethality rate of 10% (Multi-Country Monkeypox Outbreak in Non-Endemic Countries), constituting a real public health problem, considering that the disease is not directly associated with the translation of animals or humans (Kozlov, 2022), in a such manner constituting independent viral strains with different infective capacity and lethality.

The number of reported cases is alarmingly high; there is no direct link between outbreaks and travel from endemic areas, and it is unclear whether the virus has developed more human-to-human transmission capabilities, as little is known about its evolution and dynamics in general (Zumla et al., 2022). However, although, in recent years, cases have been reported in non-

endemic areas, including the 2003 and 2021 outbreaks in the United States of America and Israel, a global epidemiological pattern had never been recorded before in human history (Di Gennaro & Petrosillo, 2022).

3.3 Preventions procedures against MPX

There are numerous means of preventing Monkeypox. One way or another, contact with the epithelium or mucosa of infected individuals must be avoided, especially when the pustules become injured. Nevertheless; this is not the only procedure that must be done. According to (Thornhill et al., 2022) many sexual partners should be avoided as most new cases are occurring through sexual contact. In addition, keeping distance from objects of personal use with which the infected individual had contact and when leaving the house to crowded places, it is recommended to cover arms and legs, reducing the risk of infections.

In most cases, Monkeypox has low virulence with a lethality rate ranging from 3% to 6%. The use of antivirals such as tecovirimat, brincidofovir, and cidofovir proved to be very effective in controlling infections, combined with palliative care and good patient management, which will result in adequate control and a reduction in cases. However, in cases where there is an aggravation of the disease, the use of the drug tecovirimat is indicated (CATALENT PHARMA SOLUTIONS. HIGHLIGHTS OF PRESCRIBING INFORMATION: TPOXX (tecovirimat) capsules for oral use. Winchester, 2018). Tecovirimat inhibits the viral protein VP37 and is widely used in the fight against the genus of Orthopoxvirus such as Smallpox, Monkeypox, and Cowpox. The VP37 protein is encoded by a highly complex gene of the Orthopoxvirus family, it can be found on the surface of the virus and is present in the process of encapsulation and secretion of its protein matrix. The drug inhibits the last phase of viral replication, the interference of VP37 interaction with host cellular proteins (Rab9 GTPase and TIP47), interrupting the formation of competent encapsulated virions, necessary for proliferation in the bloodstream (Jordan et al., 2010).

There are also studies such as that of (Hraib et al., 2022) that prove the effectiveness of applying the human smallpox vaccine within 4 days after infection with Monkeypox, triggering a positive response from memory cells (T-dependent antigens) that can prevent the installation of the virus and, within 2 weeks, cook with the disease having milder symptoms, and so on not aggravating the case clinically. And as can be seen from the UKHSA Training Program for Health Workers and the work of (FINE et al., 1988), those who were previously vaccinated with the smallpox vaccine, field surveys dating from the 1980s and 1990s indicate that there is an 85% effectiveness of protection against Monkeypox and that a booster dose is sufficient to activate memory cells, B and T lymphocytes (Islam et al., 2022).

4. Discussion

Historically, because it is a variation of Smallpox, MPX was contained by vaccination in African countries, which made the population of the continent temporarily immunized against the disease. However, as smallpox ceased to be actively relevant in these countries, the new generations were not immunized through vaccination, favoring the proliferation of Monkeypox in rural areas through animal transmission, in most cases primates and small mammals. Because of this, the first cases of contamination are children and young people from non-vaccination against Smallpox, in such a way constituting the risk groups.

In the past, the literature did not have enough information regarding the epidemiological pattern of Monkeypox in a global aspect. In this way, the generalized lack of data, concerning the conclusions of the clinical results regarding the recommendations by public health agencies.

The incidence of Monkeypox is closely related to the increase in population density. This relationship occurs due to the need for territorial expansion in question, as well as the need for food to meet this unexpected increase in population, occurring respectively, the occupation and deforestation of wild areas, causing undesirable contact between humans and contaminated

animals. As well as the use of these infected animals as a source of food. Both consequences of this demographic growth were relevant to the proliferation of the virus and its zoonotic transmissibility.

In this way, the socioeconomic aspects of society will have a direct impact on the transmissibility and development of the infection in its population, since the immune system needs a balanced diet for its proper functioning, a housing system that provides piped water and sewage, in addition to access to basic health services and an appropriate educational system.

Exceptionally to other DNA genome viruses, which have their replication cycles in the nuclear compartment of infected cells, the replication cycle of Poxviruses takes place entirely in the cytoplasmic matrix of host cells. The most studied process is that of the VACV, but the basic characteristics are quite conserved among the other viruses of the Poxviridae. Although the genus Orthopoxvirus is the most studied of the family, little is known about MPXV-host cell interactions, which leaves many questions open to be adequately discussed in this article, requiring more observational time to conclude.

Vaccination has also been pointed out as the main way to combat viral infectious and contagious diseases, so that the body itself fights the injurious agents adequately, through the release of cytokines and chemokines that will determine the quality and efficiency of the inflammatory response. Cytokines and interleukins are polypeptides produced by hematopoietic cells found in the blood in response to microorganisms and other antigens, which mediate and regulate immune and inflammatory reactions, acting in a close relationship with the other cells of the immune system. In this way, cytokines have as their main function the stimulation of certain cell types so that there is information about the presence of infection. This is followed by differentiation, recruitment, activation, and chemotaxis for effective combat against the various types of aggressive agents.

Antiviral responses can be divided into two stages, the first non-specific (Innate Immune Response) and the second specific (Adaptive Immune Response), which are extremely important in combating viruses, working synergistically in the physiology of the immune system.

Although the innate immune response is the first line of defense against infections in general, both types of immunity can be self-activated, particularly in the case of viral infections, which are detected by lymphocytes and complemented by innate immune cells.

And so forth, the entire inflammatory process occurs through the stimulation of immune system cells by the production of cytokines characterized by interleukins and chemokines, proteins that, when synthesized by infected cells, activate the complement system to initiate the cascade of immunological events. Despite this, Poxviruses have developed immunomodulatory strategies, intending to weaken the host organism, through the production of proteins that interfere with the induction or activity of the complement system and the main cytokines with antiviral activities.

In the mechanisms of action of cytokines, the innate defense manages to destroy the infectious agent by developing acute inflammatory reactions with the action of macrophages, during the process, there is the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, and chemokines), in addition to mast cells, which release vasoactive amines and arachidonic acid metabolites (histamine, prostaglandin, and leukotriene). This interaction results in the clustering and migration of neutrophils towards the inflamed tissue and the leakage of plasma rich in proteins, such as C-reactive protein and C3 complement protein, synthesized by the liver in return for the endocrine action of the cytokine IL-6, establishing negative feedback between the neuroendocrine axis and the immune system (Kastenmuller et al., 2011).

As can be seen in the work of (Johnston et al., 2015), a subgroup of chemokines is directly associated with the clinical picture of the disease. In the analysis of tests, MIP-1α and MIP-1β chemokines are extremely high in milder cases of the disease, especially when compared to moderate and severe cases. Some viruses such as HIV and HCV demonstrate the previously mentioned immunomodulatory capacity, based on this, it is believed that MPX has this same capacity that directly influences resistance and continuous proliferation, resulting in a more severe picture of the disease (Mills, 2004).

The viral defense mechanisms are complex, but include well-known strategies, such as the destruction of CD4+ lymphocytes, facilitating the viral non-combat, and the immunological low that favors the appearance of secondary transmissions (Silva, 2015).

5. Final Considerations

Faced with worldwide outbreaks of Monkeypox, it became essential to prepare this study, which aimed to explain the disease, highlighting the means of transmission to promote its prevention. In light of this study, we conclude that the approach of humans to contaminated animals, due to the significant increase in population density, together with the lack of vaccination, led to the occurrence of the disease at a global level. Thus, the population's access to efficient health has become essential, so that there is effective control of this disease, through vaccines, prevention programs, and clarification of the population about the means of transmission.

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