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Monkeypox in humans – the review

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Abstract

Monkeypox is an emerging zoonotic disease caused by the monkeypox virus with a presentation similar to smallpox. Being previously endemic to Africa, now the disease is spreading across the world, causing fear of a potential next pandemic. Smallpox vaccine, previously providing cross-immunity to monkeypox virus, due to cessation of vaccinations, caused the decline in immunity against these viruses. Defined ways of transmission are animal-to-human through consumption or attack by an affected animal, human-to-human through close contact, or via respiratory droplets. Currently, there are no specific antiviral drugs and vaccine specific to monkeypox, and for symptomatic care, there are no determined guidelines.

Keywords: monkeypox, virus, pandemic

Introduction

Human monkeypox is a zoonotic disease caused by the monkeypox virus (MPXV), which belongs to the Orthopoxvirus (ORPV) genus of the Poxviridae family, consisting of other species pathogenic to humans, such as variola major virus (VARV), causing agent of smallpox, variola minor virus, and cowpox virus (CPXV) [1]. ORPVs are large viruses, ranging from 200 to 400 nm, linear double-stranded DNA (dsDNA) viruses, having genetic material of 170 to 210 kb in length that encodes about 200 proteins [2], [3]. Shortly after COVID-19, communities are uncertain if they are on the brink of a second pandemic, due to the widespread emergence of MPXV all around the globe. The objective of this review is to briefly summarize the current state of knowledge regarding epidemiology, clinical presentation, diagnosis, treatment, and prevention of monkeypox.

Epidemiology

The monkeypox virus was first discovered and isolated in 1958 due to two outbreaks of a previously unknown non-fatal pox-like disease in a monkey colony in Statens Seruminstitut in Copenhagen, Denmark [4]. The first 6 cases of human monkeypox were identified in Liberia, Nigeria and Sierra Leone between October 1970 and May 1971, the first one being a nine-month-old child from the Democratic Republic of Congo [5]. The main reservoir of the virus remains unknown, although it is believed to be mainly small mammals, specifically rodents [6], [7]. The disease caused by the monkeypox virus in both animal and human populations is mostly endemic to Central and West Africa [8]. After its discovery in the previous century, monkeypox was very rarely observed in humans, until outbreaks in 2006-07, when 20-fold incidence increases were recorded [9]. Another spike in the number of cases in endemic countries was recorded in 2017 – the number of cases rose from 16 in the previous year to 188 [10]. For several years, there has been a significant increase in the incidence of monkeypox in non-endemic countries, including those outside Africa. According to the Center for Disease Control and Prevention, the confirmed number of cases globally was 41 358, including 40 971 cases in locations that have not historically reported monkeypox (data as of 19 Aug 2022) and has reached all continents (except for Antarctica) [11]. According to the systematic review by Bunge et al. [12] the median age of the disease presentation has been 4 at its discovery in the 1970s to 21 years in recent years (2010-2019). The overall fatality rate of monkeypox was 8.7% with a significant difference between virus genetic clades – Central African 10.6% (95% CI 8.4%-13.3%) vs. West African 3.6% (95% CI 1.7%-6.8%).

Transmission

In an epidemiological modeling study by Grant et al. [13] the reproductive ratio of monkeypox was estimated to be between 1.1 and 2.4, which indicates that every infectious individual is able to infect one or two people, which displays the imminency of the monkeypox epidemic. The subject of monkeypox transmission is not fully understood, although the hypothesized modes of transmission are associated with direct contact with infected animals or humans [14]. According to Bunge et al. [12] the modes of animal-to-

human transmission may include transmission through bites or scratches from infected animals, their blood and other bodily fluids, hunting, cooking and consumption of infected animals, and contact with cutaneous or mucosal lesions. Human-to-human transmission may occur through close contact, respiratory droplets, direct contact with cutaneous lesions, or recently contaminated objects or surfaces. One of the widely spread hypotheses of human-to-human transmission mode is sexual intercourse, especially in men who have sex with men group, although according to the World Health Organisation it was not currently confirmed [15].

Clinical presentation

The incubation period for monkeypox ranges from 5-21 days, and symptoms last up to 5 weeks [16], [17]. This disease begins with the appearance of prodromal symptoms that include swollen lymph nodes, chills, fainting, fatigue, and fever. There may also be headaches and backaches, also lymphadenopathy is a feature of the majority of patients [17], [18]. Swollen lymph nodes reach a size of up to 4 cm and are tender and hard. The most commonly involved are the behind-the-ear, submandibular, cervical and inguinal nodes [19], [20]. Symptoms that also frequently occur in patients are fever and restlessness [17]. The prodromal symptoms last 2 to 4 days, followed by the development of skin lesions [18], [20]. The rash is similar to that of smallpox, it usually appears 1 to 3 days after lymphadenopathy [19]. First, the lesions are macular or papular, then develop into pustules, vesicles, ulcers, and finally scabs that fall off during the healing phase. Each stage of skin lesion may last 1-2 days. Cutaneous symptoms are usually about 0.5 cm in diameter, even reaching 1 cm.[17] It spreads centrifugally all over the body, initially affecting the face, then the hands and soles of the feet. The genitals, oral mucosa, conjunctiva and cornea may also be involved. The skin changes occur from 2 to 4 weeks [17], [19]. The severity of symptoms is generally related to the degree of exposure to the virus through transmission. The patient's underlying diseases are also a key factor [19]. In the beginning, it was thought that lymphadenopathy, which occurs in 90% of patients with monkeypox, is the only symptom distinguishing it from smallpox [17]. Although it remains the basic distinguishing feature, constituting an important element of the initial examination of a suspected patient, these two disease entities also differ in terms of other symptoms. Indicative of chicken pox, in contrast to monkeypox (MPX), are superficial lesions that mature more slowly, with irregular borders, smaller and centrally located [19]. The severity of the disease ranges from mild to severe [20]. Pregnant women, children, immunocompromised patients, and people who are not vaccinated against smallpox have an increased risk of complications and the severity of the disease [17], [19]. Complications are common and include respiratory disorders, bronchopneumonia, coinfections, keratitis with subsequent blindness, encephalitis, pharyngitis, tonsillitis, and gastrointestinal symptoms such as vomiting and diarrhea-induced dehydration [17]–[20]. The symptoms of MPX are less severe than the symptoms of smallpox, but this does not mean that the disease is not a threat to one's life. The mortality rate of this disease entity can reach up to 10% and is higher in young children and infants [17]. Usually, death occurs 2 weeks after infection. The differential diagnosis includes the aforementioned chickenpox as well as Staphylococcus skin infections, molluscum contagiosum, herpes, herpes zoster, water warts, and syphilis [16], [17].

Diagnosis

An infection with MPXV should be suspected in patients with symptoms consistent with the monkeypox clinical manifestation described above. However, epidemiological risk factors and the vaccination history should also be taken into account, including especially close contacts with suspected or diagnosed with monkeypox, as well as recent travels to endemic areas of the monkeypox activity [21]. MPXV can be identified in various assays including genetic, phenotypic and immunological methods, as well as electron microscopy. Though, these tests require high-cost equipment and well-skilled specialists in laboratory medicine, thereby making it difficult to identify the virus in low-income countries [17]. Samples can be collected as lesion exudate on a swab or crust specimens. These methods are the least invasive and samples if stored in a dark and cool environment can be kept stable for a long period [22].

The golden standard in MPXV diagnostics is nucleic acid amplification tests (NAAT), including real-time or conventional polymerase chain reaction (PCR). These assays target numerous unique sequences in the viral genome, differentiating it from other poxviruses. Presently, World Health Organization (WHO) recommends real-time quantitative PCR (RT-qPCR) alone or in combination with sequencing. However, no commercial PCR kits are available, therefore requiring a specialized facility to perform these assays [23].

Serologic tests can be used as a supportive assay in monkeypox diagnosis, especially if NAAT tests are not available. Serologic tests may be advantageous to PCR assays as they are not limited to strict targets of the viral genome, thereby allowing a detection despite constant recombination among viral variants. However, the sampling collection timing may be limiting, as serum should be collected in the early phase, though not less than 4 days after the rash onset for IgM ELISA and after 14 days for IgG ELISA. IgM-antibodies levels are in an optimal range for detection if samples are collected within a 5-77 day period after the rash onset. Developed by the Centers for Disease Control and Prevention IgM ELISA assays provided 94.8% specificity while maintaining at least 94.5% sensitivity. Whereas, IgG ELISA assays provided a sensitivity of 100% and a specificity of 88.5% [24]. Nevertheless, IgG assays cannot alone provide a definitive diagnosis for retrospective patients exposed to monkeypox, but IgM assays are more applicable for recent infections, including patients with prior vaccination [22].

Electron microscopy, histopathologic analysis and viral culture are also possible to be used in MPX diagnosis, however, these assays are not routinely used and recommended for the diagnosis of poxviruses [23], [25].

Treatment

As there are no clinically approved treatments dedicated to monkeypox infections and most cases are mild and self-limiting [26], the treatment is mostly supportive and relies on treating episodes of fever, promoting lesion healing, hemodynamic stabilization and minimizing fluid loss [27].

However, in severe disease cases, infections among pregnant individuals, immunocompromised patients and young children, antiviral drugs to treat smallpox have been

approved by the Food and Drug Administration in the United States in order to treat monkeypox [26].

Tecovirimat is the treatment of choice. It works by inhibiting the viral protein, which blocks the final steps in viral maturation, hence inhibiting the spread of the virus within the body [28]. Although the efficacy of this substance against monkeypox has not been tested on humans yet, improved survival has been reported in several studies on animals [29]. Cidofovir has been effective in treating lethal monkeypox virus infection in primates [30]. However, there is still no scientific data on the effectiveness of this antiviral drug against monkeypox in human patients [31].

Prevention

The most effective way to prevent the spread of the monkeypox virus is by implementing a multidisciplinary approach which consists of applying strict hygiene and sanitation, adequate inspection and storage of meat as well as avoidance of hunting and eating wild animals [32]. Furthermore, the collaboration between human and animal health providers is vital to investigate and administer control measures in case of a possible disease outbreak, as one-sided disease prevention is often insufficient to stop the spreading of zoonotic infections [33].

Although there is no dedicated vaccination against monkeypox available right now, prior immunization with the smallpox vaccine has been considered to show both protective effects against the monkeypox virus as well as an improvement in terms of clinical manifestations of the infection. Two vaccines against smallpox: JYNNEOS (IMVANEX in the European Union, replication-deficient live virus vaccine) and ACAM2000 (live replicating vaccine) are used against monkeypox and have shown 85% effectiveness in terms of providing cross-immunity [34]. According to the Centers for Disease Control and Prevention in the United States of America, mass vaccination against monkeypox is not recommended [26], however, it is advised to implement prophylaxis in the high-risk group, which, based on exposure type is divided into pre- and post-exposure [34].

Pre-exposure prophylaxis is recommended for individuals who are at high risk of contact with the virus due to occupational exposure: healthcare providers or laboratory personnel working with the pathogen. Post-exposure prophylaxis relies on administering the vaccination to individuals who came in close contact with confirmed cases. As the vaccination is believed to lessen the severity of symptoms only if administered between 4 and 14 days from the moment of exposure, it is advised to administer the vaccination within four days after the exposure [26].

Conclusion

With the emergence of the COVID-19 pandemic, many health organizations took into consideration the possibility of the appearance of another highly virulent pathogens, in this case, the monkeypox virus. For such an eventuality, preventive actions have to be taken, including the commencement of research to define the true range of pandemic and ways to prevent spreading, establish appropriate tools and guidelines for medical professionals to easily diagnose and treat the patient. Assessing the efficacy of existing vaccines using a modern, evidence-based approach can answer the question if developing new vaccines is

needed. Along with research regarding potential specific drugs, studies concerning the long-term effect of infection have to be considered.

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