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Perspectives

Emerging Monkeypox virus and neuroinflammatory disorders

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ARTICLE INFO

Keywords:

Monkeypox
encephalitis
neurological manifestations
cerebrospinal fluid
pediatric
neuroinflammatory disorders

ABSTRACT

Alarming situation: Monkeypox is a zoonosis caused by a double-stranded DNA virus. The virus was isolated in monkeys in 1958. The first human case was detected in Africa in 1970. It is endemic in western and central Africa. The infection has worried public health authorities around the world since May 2022 with the emergence of thousands of cases in non-African countries.

Objective: We discuss the neurological manifestations associated with monkeypox infection.

Rare and Severe Complications: Although in the current outbreak, the disease appears to be self-limiting, with predominance of focal skin lesions, complications may occur, mainly in children and immunosuppressed patients. Neurological manifestations such as encephalitis, convulsion, dizziness, pain, fatigue, visual alteration, photophobia, headache and myalgia were previously reported. Encephalitis may be due to viral invasion of the central nervous system or an immune-mediated process. In both situations, rapid recognition is extremely important with the investigation of the cerebrospinal fluid exam, which can demonstrate the local inflammatory reaction, specific IgM and, possibly viral detection, in addition to the imaging study.

Conclusions: We emphasize that health professionals should be alert to the emergence of neurological disorders associated with monkeypox infection in order to avoid sequelae and better characterize the current disease.

Introduction

Monkeypox virus is a complex, double-stranded DNA virus that belongs to the *Orthopoxvirus* genus of the *Poxviridae* family. Other members of the same genus include variola virus (the etiologic agent of smallpox), vaccinia virus, and cowpox virus, among others. Members of the *Orthopoxvirus* genus are well known for their cross-reactivity, which allowed vaccinia virus to be used successfully as the smallpox vaccine for decades (Damon 2013). Monkeypox and smallpox are very similar diseases clinically. However, smallpox, which was declared eradicated in 1980, had 30–40% case-fatality rates, whereas monkeypox has a rate of 1–10%, depending on the subtype (McCollum & Damon, 2014).

Monkeypox was first identified in monkeys used for research in Denmark in 1958, and the first human cases were detected mostly in small children in Africa in 1970 (McCollum & Damon, 2014). In subsequent years, monkeypox cases in humans have increased, mainly in the Demo-

cratic Republic of Congo, affected by the more virulent Congo-Basin subtype, and Nigeria, affected by the less virulent West Africa subtype (Bunge et al., 2022). The first cases of monkeypox in humans outside Africa occurred in the United States in 2003. Wild African rodents unknowingly infected with monkeypox virus were imported to a pet shop in Texas. The outbreak spread to another 10 states, leading to 47 infected people (Reed et al., 2004). Since then, several imported cases of monkeypox in humans have been reported in a few countries, but always with epidemiological links involving trips to African countries (Adler et al., 2022).

Since May 2022, several cases of monkeypox have been reported in non-African countries (Americas, Eastern Mediterranean, European and Western Pacific regions) with no epidemiological link to endemic countries in Africa (Vivancos et al., 2022; Duque et al., 2022; Martinez et al., 2022; CDC 2022). As of August 19, 2022, 41,358 cases and 12 deaths have been laboratory confirmed in 94 countries (CDC 2022). The out-

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<https://doi.org/10.1016/j.ijregi.2022.08.015>

Received 31 July 2022; Received in revised form 25 August 2022; Accepted 26 August 2022

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break is caused by the less virulent monkeypox virus subtype; nonetheless the number of cases has been rising daily in successful chains of transmission among humans (Vivancos et al., 2022).

In the current outbreak, monkeypox virus is spreading primarily through close (personal, skin-to-skin) and intimate contact with an individual with an active infection. Close contact involves exposure to a rash, scabs, or body fluids; or touching objects, tissues, and surfaces from a person with monkeypox. Intimate contact includes sex, touching the genitals or anus, hugs, kisses, and prolonged personal contact with someone with monkeypox. Cases predominate in gay and bisexual persons, although anyone can be susceptible to infection. The clinical manifestation has an atypical feature, with a predominance of a few lesions instead of hundreds, located in distinct areas such as the genitals (penis, testicles, labia and vagina) and anus. Skin lesions on the face, hands, feet, chest or mouth may be also found (CDC, 2022). There are macules, papules, vesicles, pustules, and crusts, which scarify. Skin lesions can progress to secondary bacterial infection. Fever, lymphadenomegaly, ocular lesions, dehydration, pneumonia, and sepsis are also reported. Viral infection is transmitted through bodily injury, bodily fluids, and even freshly handled objects. Its differential diagnosis is smallpox, chickenpox, zoster, and herpes (CDC 2022).

Neurological Complications associated with Monkeypox

The outbreak of monkeypox and the rapid spread in non-endemic countries on several continents has brought additional public health concern worldwide about the possibility of complications from the infection. Among the neurological manifestations, headache, myalgia, altered consciousness, agitation, convulsion, dizziness, pain, fatigue, visual alteration are reported. However, headache and myalgia are more frequent, being described in approximately half of infected individuals (Sepehrinezhad et al., 2022). In addition, there are reports of psychiatric manifestations such as anxiety and depression, of which the prevalence is unknown (Sepehrinezhad et al., 2022).

Encephalitis is the most serious neurological manifestation associated with monkeypox virus infection (McEntire et al., 2021). Encephalitis is the inflammation of the brain usually triggered by viruses, bacteria, fungi, neoplasms, or an autoimmune reaction. The disease is most commonly caused by a virus, which can act directly on the brain parenchyma, cause reactivation of a previous infection, or induce an autoimmune reaction, in which the immune system attacks the brain tissue (Scheld et al., 2014). The main symptoms include headache, fever and altered level of consciousness. Focal neurological deficits and seizures may also occur. The cerebrospinal fluid (CSF) test is extremely important to support the diagnosis of viral encephalitis, due to the possibility of demonstrating the local inflammatory reaction and the identification of the etiological agent. The CSF profile is characterized by predominantly mononuclear pleocytosis (10–200 cells/ μ l) or normal cell count (< 5 cells/ μ l), occasionally neutrophilic predominance in early stages, elevated protein (< 100 mg/dL), and glucose and lactate are usually normal. Regarding viral tests, molecular testing by nucleic acid amplification (PCR) has obtained more sensitive and faster results than viral culture for the early diagnosis of viral encephalitis, although it may have some limitations, depending on the viral agent and the duration of symptoms. The detection of specific IgM in serum/CSF and specific intrathecal synthesis of antibodies may be helpful, especially in the later stages of the CNS infection, when PCR is already negative (Puccioni-Sohler et al., 2018).

Reports of encephalitis have occurred in children in previous outbreaks of monkeypox infection (Badenoch et al., 2022). In one of the cases, a 3-year-old child progressed to coma and died on the second day of hospitalization (Ježek et al., 1987; Badenoch et al., 2022). The other case occurred during the 2003 monkeypox outbreak in the United States (Sejvar et al., 2004). This was a 6-year-old girl, without comorbidities, not vaccinated for chickenpox. After contact with 2 prairie dogs from Gambia, she presented monkeypox infection with extensive skin le-

sions, complicated with encephalitis. She evolved with fever,odynophagia, headache, cervical lymphadenopathy, drowsiness, and generalized tonic-clonic seizure. The first CSF exam showed pleocytosis, with a predominance of polymorphonuclear cells (60%). There was a change in the CSF pattern in the control exam, with a predominance of lymphocytes (80%), normal glucose, and protein unchanged. The electroencephalogram had diffuse slowing. Cranial magnetic imaging showed diffuse cortical edema in the thalamus and brainstem, meningeal enhancement, and signal alteration in the left thalamus and right posterior parietal cortex. The diagnosis of monkeypox was confirmed by skin biopsy with immunohistochemistry and blood serology (specific reactive IgG and IgM). CSF was PCR-negative for virus, but with positive specific IgM suggestive of intrathecal antibody production. The patient was discharged from the hospital with progressive improvement of the neurological condition and evolved with normal neurological examination without any sequelae (Sejvar et al., 2004).

There are reports of post-mortem findings of perivenular demyelination in the brains of patients who died due to smallpox encephalitis (Marsden 1934). Cases of acute disseminated encephalomyelitis (ADEM) seen on cranial magnetic resonance are described after smallpox vaccination, and CSF exams showed an aseptic meningitis pattern, indicating immune-mediated pathogenesis (Sejva et al., 2005). ADEM is a rare monophasic autoimmune disease, which courses with diffuse inflammation and demyelination of the central nervous system (CNS), usually after infection or vaccination. It is characterized by encephalopathy and multifocal neurological deficits (Scheld et al., 2014).

According to the WHO (2022), the greatest chance of severe presentations of monkeypox virus infection would be in children, mainly under 8 years of age, the immunosuppressed (those with HIV, hematological malignancies, use of immunosuppressive drugs such as corticosteroids, organ transplant patients, autoimmune disease, or innate immunodeficiencies), presence of dermatological diseases that affect the integrity of the skin barrier (acne, atopic dermatitis, varicella-zoster virus, herpes simplex virus, contact dermatitis, psoriasis), pregnant or lactating women, patients with comorbidities or complications during hospitalization (World Health Organization 2022), and patients unvaccinated against smallpox (Ježek et al., 1987). The course of the disease appears to have a fatal outcome mainly in children, specifically those who have not received smallpox vaccination (McEntire et al., 2021; Ježek et al., 1987).

Challenges for Public Health Programs

The current smallpox outbreak was declared a Public Health Emergency of International Concern by the WHO on July 23, 2022 (World Health Organization 2022).

In recent years, urban agglomeration and human invasion of wild areas and reserves has been increasing, leading to a greater risk of zoonotic infections, particularly of viral origin and with greater virulence (Damaso, 2022). Nevertheless, the viral subtype responsible for the current outbreak of monkeypox appears to be less virulent than previously reported, and consequently, the clinical presentation of the infection has shown self-limiting features. However, the process of virus fitness and evolution in humans requires close vigilance. New tropisms for specific organs could emerge, such as the nervous system, and neurotropic variants could be of potential harm to humans. In fact, neurological manifestations may occur in the course of infection by monkeypox virus, including reports, although infrequent, of severe and fatal forms such as encephalitis, which recently occurred in Spain, as reported on July 28, 2022 (Ministerio de Sanidad, 2022). The risk for children, pregnant women, and immunocompromised people is higher than in other groups, although the two deaths in Spain were not associated with any other comorbidities. The diagnosis of encephalitis is challenging, considering the variety of etiologic agents and the severity of the disease. Despite extensive investigation, about 40–70% of cases remain undiagnosed (Scheld et al., 2014). On the other hand, in cases where the

etiologic agent has been identified, there may be no specific treatment, as in encephalitis associated with monkeypox infection. It is a condition that can lead to death or sequelae such as permanent cognitive and motor deficits.

Neurological complications are not the only burden to the health system following monkeypox infection. The short supplies of vaccines and antivirals available for monkeypox prophylaxis and treatment are quite concerning, particularly for developing and low-income countries (Damaso, 2022). This issue needs to be addressed urgently before the number of severe cases increases. Although mass vaccination is not required, specific population groups are at higher risk and need further protection—such as men who have sex with men (MSM), which corresponds to > 95% of the infected population worldwide (Tarín-Vicente et al., 2022; Philpott et al., 2022; Thornhill et al., 2022). While stigmatization needs to be drastically refuted, it is important to deliver to MSM groups the correct information on the transmission mode and means to prevent infection, and the public health system has an essential role in establishing this communication.

Conclusions

Due to the epidemiological profile with an increasing number of cases associated with the risk of viral invasion of the CNS or immune-mediated neurological manifestations, it is fundamental to train infectious health teams, especially neurologists, infectious disease specialists and pediatricians, to be aware of neurological sign alerts (such as severe headache, convulsion, visual alteration, altered level of consciousness, or motor deficit) in the presence of monkeypox infection and implement adequate investigation of the neurological picture. In cases with suspected encephalitis, the CSF and brain imaging study are mandatory. The CSF exam may demonstrate local inflammation, viral detection by PCR technique, or the presence of specific IgM, and excludes other infectious agents. As the virological tests have limited sensitivity, the diagnosis of monkeypox infection should be confirmed by performing a PCR assay on samples from skin lesions as well as by identifying specific IgM in serum. Magnetic resonance is the imaging method of choice for evaluating viral encephalitis. In general, confluent lesions with a variable mass effect are observed. These early measures would avoid delaying diagnosis and unnecessary antimicrobial treatment, disabling neurological sequelae, and compromising the individual's quality of life, in addition to allowing a better characterization of the neurological manifestations of monkeypox virus infection.

Conflict of Interest

The author has no conflicts of interest to report.

Funding Source

This work did not receive any grant from funding agencies.

Ethical Approval Statement

Approval was not required.

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