Neurologic Complications of Smallpox and Monkeypox
A Review

B. Jeanne Billioux, MD; Oliver Tshiani Mbaya, MD; James Sejvar, MD; Avindra Nath, MD

IMPORTANCE Orthopox viruses include smallpox virus, a once feared but now eradicated virus, as well as monkeypox virus. Monkeypox is an emerging virus initially isolated in 1958, previously unrecognized outside sub-Saharan Africa until a worldwide outbreak in May 2022. It is important to review known neurologic consequences of both these viruses, as complications of smallpox may be relevant to monkeypox, though complications of monkeypox may be rarer and perhaps less severe.

OBSERVATIONS This was a literature review of the known neurologic complications of smallpox, which include encephalitis, transverse myelitis, and acute disseminated encephalomyelitis among others; historical complications of smallpox vaccination, including postvaccinal encephalomyelitis; and the known neurologic complications of monkeypox, which include headaches and mood disturbances, as well as rare presentations of encephalitis, transverse myelitis, and seizures. Of concern is the possibility of viral persistence and systemic complications in immunocompromised individuals. Also provided were considerations for diagnosis, current treatment, and prevention of monkeypox.

CONCLUSIONS AND RELEVANCE Monkeypox should be considered in high-risk populations who present with neurologic syndromes. Diagnosis may require serology and polymerase chain reaction testing of blood and spinal fluid. Antiviral therapy should be initiated early in the course of the illness.

JAMA Neurol. doi:10.1001/jamaneurol.2022.3491
Published online September 20, 2022.

The recent global emergence of monkeypox1 has raised fears of another pandemic immediately following the COVID-19 pandemic. Although the COVID-19 pandemic is the worst pandemic in a century, the recent past has seen several major pandemics, including Zika, Ebola, Dengue, West Nile, and AIDS. A common thread to these pandemics is the long-term neurologic complications such as post–COVID-19 conditions, congenital Zika syndrome, post-Ebola syndrome, West Nile encephalitis, and HIV-associated neurocognitive disorders. These complications have major socioeconomic effects and are feared by the public. Yet often these manifestations go unrecognized, initially masked by the acute systemic involvement by the infection and later attributed to end-organ damage or to pandemic-related psychosocial stresses. For these reasons, we have reviewed the literature on orthopox viruses, which include both smallpox and monkeypox, with a focus on neurologic complications.

Orthopox Overview

Orthopoxviruses are zoonotic, phylogenetically related, double-stranded DNA viruses with reservoirs in wild and domestic mammals, food animals, and rodents. Most of these viruses infect only animals and do not cause disease in humans, although some may be zoonotically transmitted to humans by respiratory droplets or by direct contact with skin lesions or contaminated fomites. There are 17 known species of orthopoxviruses, with new emerging species frequently reported. Animal-to-human transmission has been reported for 8 of these viruses and human-to-human transmission for 5 (variola, monkeypox, vaccinia, cowpox, and buffalopox).2 Monkeypox is the most common cause of human infections. Variola or smallpox does not have an animal reservoir, which in part made its successful eradication possible. The natural reservoir of monkeypox, despite its name, are rodents in Africa (Table 1). Its spread to Europe and the US has occurred either through importation of African rodents or through human-to-human transmission. Orthopoxviruses are large virions; their DNA is 170 to 250 kilobases in length, which are folded onto themselves to give the virion a bricklike structure. Replication occurs in the cytoplasm; hence, infected cells show cytoplasmic inclusion bodies.

Smallpox

History of Smallpox and Eradication

Smallpox was a highly feared, disfiguring disease known to humans for thousands of years, until its eradication in 1980. There are descriptions of Egyptian mummies with rashes similar to that of smallpox.3 Writings detail smallpox outbreaks in Asia, Africa, and Europe as early as the fifth century CE. Coinciding with the Spanish

10 Center Dr, Bldg 10, Room 7C-103, Bethesda, MD 20892
(natha@ninds.nih.gov).

Author Affiliations: National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland (Billioux, Nath); Institut National de Recherche Biomédicale, Kinshasa, Democratic Republic of Congo (Mbaya); Centers for Disease Control and Prevention, Atlanta, Georgia (Sejvar).

Corresponding Author: Avindra Nath, MD, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Dr, Bldg 10, Room 7C-103, Bethesda, MD 20892 (natha@ninds.nih.gov).
conquest, smallpox devastated the Incan and Aztec civilizations in North and South America, with 3 to 4 million disease-related deaths in the 16th century. Smallpox was introduced to New England in the early 1600s by European settlers, causing epidemics in Boston, Massachusetts, and New York during the 17th century. Smallpox caused epidemic disease throughout Europe in the Middle Ages and into the 1800s, even after the introduction of Edward Jenner’s successful preventive vaccine using inoculation with cowpox in 1796. In the early 1800s, Benjamin Waterhouse promoted Jenner’s vaccine in America and conducted what is considered one of the first controlled clinical trials with the vaccine. In the mid-20th century, improvements in vaccine production and improvements in vaccine delivery led to successful mass vaccination campaigns. The World Health Organization (WHO) in 1966 started a campaign to eradicate smallpox. The last naturally occurring case of smallpox was in 1977, and the WHO declared smallpox eradicated in 1980.

Clinical Manifestations of Smallpox

There are 2 variants, variola major and variola minor, with variola major causing more severe disease with higher mortality rates. Smallpox has an incubation period of 7 to 17 days, followed by a prodrome of fever, headache, and backache. Temperatures can reach higher than 40 °C (104 °F), subsiding gradually over several days. The following eruptive phase is characterized by enanthematous lesions involving mucous membranes of the mouth, tongue, and oropharynx. The exanthema phase follows about a day later, with skin lesions starting peripherally on the face and extremities, and subsequently more centrally on the entire body within 1 to 2 days, known as a centrifugal pattern. The rash starts as small red macules, becoming 2- to 3-mm papules over 1 to 2 days, then 2- to 5-mm vesicles after another 1 to 2 days. These vesicles transform into 4- to 6-mm pustules between 4 to 7 days after the rash onset, last between 5 to 8 days, then umbilicate and crust. A characteristic feature of these lesions is that generally they are all at the same stage. This feature and the centrifugal pattern of the lesions are considered important clinical characteristics that are useful in discerning the lesions from those of varicella. The WHO classified the clinical forms of smallpox into 5 subtypes: ordinary, modified, variola sine eruption, flat, and hemorrhagic. Ordinary smallpox is the most common with a 30% fatality rate. Modified and variola sine eruption are mild cases that occurred in patients previously vaccinated. Flat and hemorrhagic smallpox were rare but severe forms, with up to 97% case fatality rates. Complications of smallpox include bronchopneumonia, viral keratitis (which could lead to panophthalmitis and blindness), and arthritis, including osteomyelitis variolosa, in approximately 2% to 5% of children, causing joint deformities.

Neurologic Complications With Smallpox

Smallpox may lead to a variety of neurologic complications, though reports are sparse (Table 2). Headaches at onset are very common. Backaches are typical in the prodrome, affecting up to 90% of patients. Delirium or encephalopathy can accompany the disease in about 15% of patients during the febrile stage. Febrile seizures can occur in about 7% of children younger than 5 years. Encephalitis may occur in approximately 1 in 500 cases of smallpox, characterized by decreased levels of consciousness. Cerebrospinal fluid (CSF) is characterized by elevated opening pressure, mild lymphocytic pleocytosis, which may be neutrophilic early on, nor-

---

**Table 1. Orthopox Viruses That Infect Humans**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Human-to-human transmission</th>
<th>Animal-to-human transmission</th>
<th>Major animal host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variola (smallpox)</td>
<td>Yes</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Monkeypox</td>
<td>Yes</td>
<td>Yes</td>
<td>Rodents</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>Yes</td>
<td>Yes</td>
<td>Cattle</td>
</tr>
<tr>
<td>Cowpox</td>
<td>Yes</td>
<td>Yes</td>
<td>Cats, rodents, cattle</td>
</tr>
<tr>
<td>Buffaloopx</td>
<td>Yes</td>
<td>Yes</td>
<td>Cattle</td>
</tr>
<tr>
<td>Alkhmeta virus</td>
<td>No</td>
<td>Yes</td>
<td>Small mammals, cattle</td>
</tr>
<tr>
<td>Alaskapox</td>
<td>No</td>
<td>Yes</td>
<td>Small mammals</td>
</tr>
<tr>
<td>Camelpox</td>
<td>No</td>
<td>Yes</td>
<td>Camels</td>
</tr>
<tr>
<td>Horsepox</td>
<td>No</td>
<td>Yes</td>
<td>Horses, cattle</td>
</tr>
</tbody>
</table>

**Table 2. Neurologic Manifestations of Orthopox Viruses**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Smallpox</th>
<th>Vaccinia vaccine</th>
<th>Monkeypox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Febrile seizures/encephalopathy</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Viral encephalitis</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ADEM</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acute flaccid paralysis</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Post viral cerebellar signs</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviation: ADEM, acute disseminated encephalomyelitis.

* The + indicates presence of the clinical syndrome; the − indicates absence of the clinical syndrome.

b Presumed viral encephalitis; viral isolation was not attempted.
neurologic complications, particularly seizures. Seizures were the most common adverse effect, occurring in about 25% of vaccinees. Other adverse effects included encephalitis, meningitis, myelitis, and optic neuritis. The most frequent adverse effects were meningitis and encephalitis, with a combined incidence of about 10%.

Cryptic transmission has been described in patients presenting with a generalized vesiculopustular rash in the Demographic Republic of Congo (DRC) and other western African countries. The disease was clinically similar to smallpox, and sporadic cases were reported in Central and Western Africa, all areas in which no smallpox had been reported for more than 1 year. Monkeypox has largely been a disease confined to Central and West Africa, occurring in intermittent outbreaks with occasional small exported outbreaks in Western countries, including the US in 2003, the UK in 2018, and Israel in 2018. However, monkeypox has come to global prominence since the spring of 2022 with the onset of an international outbreak affecting more than 40,000 people in more than 80 countries.

Epidemiology and Transmission

The initial transmission mode is from animals to humans. Direct contact with infected animals or possible ingestion of inadequately cooked meat were the main modes of transmission in past outbreaks. Several animals have been implicated in the primary transmission of monkeypox infection. However, epidemiologic investigations defined a close link with forest-dwelling rodents (eg, Gambian pouched rat, rope squirrel). Human-to-human transmission was also a driver in past outbreaks, as illustrated by the 1996 to 1997 outbreak in the DRC when 8% to 15% of contacts reported respiratory droplets, contact with mucocutaneous lesions, or fomites as modes of secondary transmission. Human-to-human spread is driving the current outbreak of MPXV, particularly through sexual contact, although other forms of close contact with infected patients are also occurring. There is also concern about the possible spread to pets and other animals, which could result in a zoonotic reservoir. Recent studies show that monkeypox viral DNA can be detected in skin lesions and also in saliva, urine, fecal matter, and semen. Viral culture of these fluids has not been performed; however, viral shedding in a variety of fluids indicates that the virus may have other routes of infectivity that need to be explored.
Clades
Until recently, MPXV was recognized as having 2 genetically different clades, the Congo Basin (CB) clade and the West African (WA) clade, with different clinical expressions and geographic locations. The WA clade was less severe than the CB clade with a case fatality rate of 0% to 6%, whereas the CB clade presented a mortality of 11%, which was higher in children (approximately 17%).25 Recently, a third clade was recognized as a subset of the WA clade. To make the naming conventions of MPXV clades less stigmatizing, they have been renamed as clade 1 (CB clade) and clades 2 and 3 (WA clades).26

Outbreaks
Worldwide, the DRC has the highest number of cases with more than 1000 cases each year since 2005. The disease is endemic in the DRC, with epidemic fluctuations. A big outbreak occurred in the province of Sankuru (Kole) in 1996 and is ongoing in the Maniema province (Tunda) since November 2021. In May 2022, an unprecedented flare-up of monkeypox was identified in Europe, North America, and Australia (Figure 1). Sequencing analysis identified MPXV clade 3 (formerly a subset of the WA clade) virus as the cause.27 Disease transmission was largely among men who have sex with men,28-30 suggesting the potential for sexual transmission. As of August 22, 2022, there were 14 594 cases reported in the US.1

Clinical Manifestations
The clinical features of the disease are similar to those of smallpox, preceded by an incubation period from 4 to 21 days and characterized by 2 phases. The prodromal phase includes general signs like fever, headache, chills, sweats, sore throat, myalgias, prostration, and lymphadenopathy (cervical, submandibular, axillary, inguinal). Lymphadenopathy represents the pathognomonic sign of the disease and differentiates monkeypox from smallpox and other viral rash illnesses, including chickenpox. However, in some cases, clinical features alone may not be sufficient to distinguish these illnesses.31 The differential diagnosis of the rash should also include herpes simplex type 1, syphilis, and molluscum contagiosum. Hence, patients should undergo a complete skin and mucosal examination. The rash phase lasts between 2 and 4 weeks. Skin lesions are characteristic with uniform progression from macules to papules, vesicles, pustules, umbilication, crusting, and desquamation (Figure 2). Lesions typically have a centrifugal distribution. Extracutaneous findings include gastrointestinal symptoms. Complications may occur due to bacterial superinfection and dehydration.32 Other complications may include sepsis, neurologic impairment, or ocular damage. Subclinical infection and asymptomatic cases occur at a rate of approximately 30%.32 The current outbreak of monkeypox in Western countries seems to be a milder disease, with some key differences from the classic description of monkeypox.32 Skin eruptions are mostly localized to the site of inoculation, including the genital, perianal, and oral regions. Additionally, the presenting symptom may be skin lesions, as opposed to the usual prodromal presentation. Some cases have asynchrony of lesions, in contrast to classic presentations. Lymphadenopathy may be limited to the inguinal region, and complications include proctitis, epiglottitis, and myocarditis.23,24,28-30 Several larger cohorts of patients with monkeypox have noted a rate of people living with HIV up to or greater than 40%, with the vast majority of this subgroup well controlled on antiretroviral therapy.28,30,33 Coinfections with other sexually transmitted infections, including gonorrhea, chlamydia, and syphilis, among others, have been described, with 1 cohort noting 29% with concomitant sexually transmitted infections.30

Neurologic Complications of Monkeypox
Very few neurologic complications of monkeypox have been described (Table 2). Headache is a common presenting feature in both clades 1 and 2.24,35 Mood disturbance, including depression and anxiety, and neuropathic pain are frequent.36,37 The skin lesions themselves may cause painful sores and, depending on the site involved, can cause dysphagia, rectal pain with anal fissures, etc. It is not clear if some of the pain may be dermatomal—similar to that seen with varicella zoster—but the pain can be severe. Conjunctivitis occurred in approximately 20% of patients in a recent outbreak in the DRC, which could lead to decreased vision. This could also be a po-
tential site for virologic seeding into the central nervous system. Monkeypox rarely causes encephalitis. A 3-year-old unvaccinated girl, during the 1980 to 1985 Zaire monkeypox outbreak, developed encephalitis, became comatose, and died 2 days after hospital admission. During the brief outbreak in the midwestern US in 2003 and propagated by a pet prairie dog, another 6-year-old girl had prodromal symptoms of headache, fever, and malaise, with a rash 2 days later. Seven days after initial symptoms, she developed decreased responsiveness, rigidity, dilated pupils, disc edema, and bilateral Babinski signs. MRI revealed meningeal enhancement, right parietal and left thalamic signal abnormality, and diffuse edema involving the cortex, thalamus, and brain stem. CSF revealed mild pleocytosis (21 cells/mm³) with a neutrophilic predominance (60%) and normal protein and glucose levels. CSF was negative for MPXV DNA by PCR testing. With supportive care, the patient improved and was discharged 2 weeks after admission. She had no neurologic deficits 1 month later. Three cases of encephalitis with seizures occurred in a cohort of 40 monkeypox cases in Nigeria, including 2 patients (a 28-day-old infant and a 43-year-old man with HIV/AIDS) who subsequently died. It is worth noting that the first case of encephalitis was associated with the clade 1, whereas the others were associated with clade 2. During the current outbreak, 3 cases of encephalitis have been reported in 2 male Spanish patients and 1 young male Indian patient, all of whom subsequently died. In the 2 Spanish patients, MPXV DNA was detected by PCR in the CSF, as well as antiorthopox immunoglobulin M (IgM) with enzyme-linked immunosorbent assay (ELISA).

Management

Because the infection is transmitted through sexual and close contact, it is important to investigate for coinfections with other sexually transmitted diseases as well. As noted previously, in the current outbreak, approximately 40% of individuals are coinfected with HIV. All patients should undergo serology or PCR testing of the vesicular fluid for MPXV through the local health department until commercial testing becomes available, noted in the guidelines by the WHO for general management of patients with monkeypox. In cases of suspected MPXV-related neuroinvasive disease, viral PCR should be attempted in CSF, although IgM antibodies in the CSF may persist longer and may be diagnostic. To date, some investigational antiviral medications have demonstrated activity against MPXV in vitro and in animal models, but none have been evaluated in a controlled clinical trial. The most promising is tecovirimat (ST-246), developed by SIGA Technologies Inc, and approved by the US Food and Drug Administration (FDA) for the treatment of smallpox. Tecovirimat is given as a 200-mg oral capsule or intravenously. The oral dose for adults is typically 600 mg, twice per day, for 14 days. It inhibits p37, an orthopox envelope-wrapping protein. Tecovirimat has been safely used in
some cases in the US and Europe.36,47 Brincidofovir (lipid conjugate of cidofovir) was approved by the FDA in June 2021 under the agency’s animal rule treatment of human smallpox disease caused by variola virus in adult and pediatric patients, including neonates.48 Brincidofovir is an orthopoxvirus nucleotide analog DNA polymerase inhibitor. It is given as 200 mg, once weekly, for 2 doses (days 1 and 8). Efficacy studies conducted in rabbitpox and mousepox models showed improvement and better survival,49 but efficacy in monkeypox is unclear. Cidofovir inhibits the DNA synthesis of DNA viruses, like cytomegalovirus, and protects mice from a lethal respiratory infection with vaccinia.50,51 Thus, tecovirimat, brincidofovir, and cidofovir may be effective in the treatment and short-term prophylaxis of smallpox and related poxvirus infections in humans. An in vitro screen of 132 clinically approved drugs identified atovaquone, mefloquine, and molnupiravir with efficacy against MPXV.52

Supportive and symptomatic care, which may be the only resources available for patients in resource-limited settings, play an important role in the management of monkeypox. Pain management is key and requires topical agents, oral medications, or nerve blocks. Painful lesions may respond to antiviral treatments; hence, access to them is crucial. In patients who are immunocompromised or have atypical presentations, the possibility of viral infection of the central nervous system should be considered. In any patient presenting with an acute neurologic illness in the setting of a possible viral infection, it is critical to collect multiple biological specimens at initial encounter to determine the etiologic agent since viremia occurs in the early phase of the illness. CSF should be obtained if there is no contraindication for lumbar puncture and assessed for MPXV DNA by PCR testing and orthopoxvirus IgM, if possible. If skin lesions are present, then vesicular fluid and skin biopsy should also be obtained. If patients have typical presentations of ADEM or transverse myelitis, treatment with high-dose corticosteroids may be warranted. Similarly, Guillain-Barré syndrome should be treated with plasmapheresis or intravenous immunoglobulins. Vaccinia-specific immunoglobulins do not have any role in treatment of postvaccine encephalitis.

Prevention

Smallpox vaccines induce cross-reactive antibodies that protect against infection from other Orthopoxvirus species. Live vaccinia virus vaccine (first generation), used during the smallpox eradication program, was 85% effective against monkeypox infection.53 This vaccine may cause serious adverse effects (including neurologic adverse effects, as detailed previously) and is contraindicated in pregnant women, immunocompromised people, and people with eczema.54 The second- (ACAM2000), and third- (Jynneos, also known as Imvanex or Imvamune) generation vaccinia vaccines have reduced adverse effects and simplified administration; however, it would not be surprising if mass inoculation resulted in some cases with neuroinflammatory manifestations, such as Guillain-Barré syndrome, myelitis, or encephalitis. The Advisory Committee on Immunization Practices (ACIP) recommended preexposure prophylaxis with ACAM2000 in 2015. Jynneos, a replication-deficient live vaccinia virus was licensed in the US in 2019. On November 3, 2021, ACIP recommended Jynneos preexposure prophylaxis as an alternative to ACAM2000 for persons at risk for exposure to orthopoxvirus.54

Conclusions

In the wake of the current multinational outbreak of monkeypox, it is evident that many aspects of this disease are understudied. This includes neurologic complications and sequelae and their management. Hence, it is important to review the literature for not only MPXV but also other orthopoxviruses, such as smallpox virus, to better understand the potential of these complications. To date, few major neurologic complications have been reported with the current clade 3 outbreak. However, based on known neurologic complications of orthopoxviruses, we must be prepared for the possibility of viral encephalitis, myelitis, ADEM, Guillain-Barré syndrome, neuropathic pain, and others, and treat them accordingly. Particular attention should be paid to patients with immunocompromised conditions, such as HIV/AIDS, as it may facilitate viral neurovasculopathy. At more than 40,000 cases worldwide and spreading,1 neurologic complications are to be expected. Preventive measures including third-generation vaccinia vaccines are available but in short supply. Although they are safer than previous vaccines, healthcare providers should be vigilant for possible neurologic adverse reactions, as these vaccines are reaching a wide population.
Neurologic Complications of Smallpox and Monkeypox


JAMA Neurology Published online September 20, 2022

© 2022 American Medical Association. All rights reserved.