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# Neuroinflammatory disorders of the central nervous system associated with monkeypox virus: a systematic review and call to action

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## Abstract

**Background** Monkeypox virus (MPXV) has emerged as a significant global health concern with outbreaks worldwide. While MPXV is primarily known for its dermatological and systemic manifestations, it can also cause central nervous system (CNS) complications. This systematic review describes the demographic, clinical, diagnostic, and therapeutic characteristics of MPXV-associated CNS neuroinflammatory disorders.

**Methods** We systematically reviewed the literature to identify cases of MPXV-associated CNS neuroinflammatory disorders. Data on demographics, systemic and neurological manifestations, diagnostic methods, treatment strategies, and outcomes were extracted and analyzed.

**Results** Eighteen cases of MPXV-associated neuroinflammatory disorders were identified. The mean age of patients was 27.8 years (range: 28 days to 43 years), with a male predominance (66.7%). Diagnosis included The most common diagnoses were acute disseminated encephalomyelitis in nine cases (50.0%), encephalitis/meningoencephalitis in seven cases (38.9%, isolated transverse myelitis in one case (5.6%), and transverse myelitis with encephalitis in one case (5.6%). The latency between the onset of systemic symptoms and neurological involvement averaged 6.2 days. MPXV detection was confirmed in 13 of 18 (72.2%) cases, primarily using quantitative real-time polymerase chain reaction from various biological specimens. Among the 12 cases with documented treatment, the most commonly administered therapies were tecovirimat (58.3%) and intravenous methyl-prednisolone (66.7%). Outcomes were reported in 17 cases, with complete recovery in 29.4%, partial recovery in 41.2%, and death in 29.4% of patients.

**Conclusions** MPXV-associated neuroinflammatory disorders of the CNS are rare but cause significant complications. The findings underscore the need for clinical vigilance, advanced diagnostic approaches, and targeted therapeutic strategies. Further research is essential to elucidate mechanisms underlying MPXV neurovirulence and develop effective treatments for these life-threatening conditions.

**Keywords** Monkeypox virus, Central nervous system, Neuroinflammatory disorders, Encephalitis, Encephalomyelitis, Meningoencephalitis, Transverse myelitis, qRT-PCR, Cerebrospinal fluid, Magnetic resonance imaging, Antiviral therapy, Immunomodulation, Systematic review

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## Background

Monkeypox virus (MPXV), a zoonotic pathogen of the *Orthopoxvirus* genus within the Poxviridae family, has evolved from being primarily endemic in Central and West Africa to becoming a growing global health concern. The resurgence of MPXV gained attention in 2017 following a significant outbreak in Nigeria and escalated further in 2022, prompting the World Health Organization to declare it a Public Health Emergency of International Concern [1]. Recent data reveal concerning trends: as highlighted by Bunge et al. [2], the total number of human MPXV cases has increased, particularly in the Democratic Republic of the Congo, where the median age at diagnosis rose from 4 years in the 1970s to 21 years in later years of observation.

The MPXV is classified into two primary clades: the Central African (Congo Basin) clade (clade I) and the West African clade (clade II), each with distinct epidemiological and clinical features [3]. The Central African clade exhibits higher virulence, with a case fatality rate of up to 10.6%, compared to 3.6% for the West African clade [2–4]. Recent outbreaks, particularly the global emergence of clade IIb (a sub-lineage of the West African clade) since 2022, have highlighted significant shifts in transmission patterns, with human-to-human spread dominating and milder clinical presentations observed [5]. Emerging sub-lineages, such as the clade I variant identified by Khan et al. [6], further, emphasize the need for ongoing research into MPXV evolution and its impact on public health.

While MPXV is primarily known for its characteristic dermatological manifestations, such as rash and skin lesions, emerging evidence suggests that the infection can lead to severe neurological complications. Khan et al. [6] conducted a systematic review of 22 studies that reported various neurological symptoms associated with MPXV infection. Their findings revealed that the most commonly reported neurological manifestations included headache (48.8%) and myalgia (27.5%), while severe complications like encephalitis (0.8%), seizures (0.3%), encephalomyelitis (0.2%), coma 0.1%), and transverse myelitis (0.1%) were also documented, underscoring the spectrum of neurological complications associated with MPXV.

Similarly, Badenoch et al. [7] performed a meta-analysis of 19 studies involving 1512 participants, identifying pooled prevalence rates for seizures (2.7%), confusion (2.4%), and encephalitis (2.0%). Despite the relatively low incidence of severe complications, these findings emphasize the need for heightened clinical vigilance. This study also highlighted substantial variability in reported data, likely due to heterogeneity across studies, complicating the determination of definitive prevalence rates for MPXV-related neuropsychiatric conditions.

Neuroinflammatory disorders of the central nervous system (CNS) encompass a diverse spectrum of pathological conditions characterized by CNS inflammation. These conditions frequently involve the activation of glial cells, such as microglia and astrocytes, alongside immune system dysregulation, resulting in neuronal damage and dysfunction. Neuroinflammatory processes are integral to the pathogenesis of numerous neuroinvasive diseases, with systemic infections like SARS-CoV-2, West Nile virus, and other pathogens playing significant roles in driving these mechanisms [8–11].

Despite these insights, the neuroinflammatory processes associated with MPXV infection remain poorly understood. The mechanisms underlying viral invasion, replication, and immune-mediated damage within the CNS are largely unexplored, underscoring the need for further investigation into this emerging pathogen.

The purpose of this systematic review is to synthesize evidence on de novo MPXV-mediated neuroinflammatory manifestations of the CNS. This paper provides a comprehensive overview of the current understanding of MPXV's neuro-inflammatory complications, with a focus on pathogenesis, clinical manifestations, and immunological correlates of CNS involvement. By consolidating these findings, the review aims to highlight the mechanisms underlying MPXV-induced neuroinflammation and its potential clinical consequences.

Understanding the neuroimmunological aspects of MPXV infection is critical for developing effective therapeutic strategies, and management plans to mitigate its impact. As the global MPXV situation continues to evolve, this review serves as a resource for clinicians, researchers, and public health officials, shedding light on the neurological complications associated with MPXV infection. Furthermore, it aims to guide future research directions in this emerging field, emphasizing the importance of targeted interventions and improved surveillance for MPXV-associated neuroinflammatory disorders.

## Methods

### Design

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (CRD42024583269). We included studies relevant to MPXV infection cases with suspected or confirmed CNS inflammatory disorders.

### Search strategy

We utilized pre-specified search strategies to retrieve data from PubMed, EMBASE, Cochrane Library, Web of Science, and PsycINFO databases up to September

10, 2024. The search strategy integrated terms associated with MPXV infection and CNS inflammatory manifestations. Relevant Medical Subject Headings (MeSH) and keywords were employed, including Mpox (monkeypox), monkeypox virus, MPV, central nervous system diseases, neurological disorder, neurologic manifestations, neurogenic inflammation, encephalitis, meningitis, myelitis, demyelination, demyelinating autoimmune diseases, CNS, spinal cord diseases, transverse myelitis, multiple sclerosis, meningoencephalitis, and encephalomyelitis.

We also hand-searched additional MPXV-specific articles using reference lists of selected studies, relevant journal websites, and pre-print servers (medRxiv, bioRxiv, and pre-prints.org) from 2022 to September 10, 2024. To mitigate publication bias, we examined references of all studies potentially missed in the electronic search. Context experts also searched gray literature for relevant articles.

#### Study selection criteria

We included all peer-reviewed and pre-print cohort studies, case–control studies, case series, and case reports that adhered to our pre-defined inclusion and exclusion criteria.

Inclusion criteria: Studies were included if they met the following conditions: (i) focused on MPXV-positive patients with suspected or confirmed neuroinflammatory diseases of the CNS; (ii) investigated associations between MPXV infection and neuroimmune disorders involving the brain or spinal cord; and (iii) were published in English.

Exclusion criteria: Studies were excluded if they involved individuals with pre-existing primary demyelinating disorders, lacked confirmed MPXV infection, or were published in languages other than English. Review articles, viewpoints, perspectives, commentaries, and studies that did not provide data on neuroimmune diseases affecting the CNS were also excluded.

#### Data extraction

To ensure a standardized interpretation of the inclusion and exclusion criteria, three reviewers (GB, VS, and PS) conducted calibration exercises using a sample set of studies before initiating the screening process. Discrepancies identified during these sessions were resolved through discussion, resulting in further refinement of the criteria.

During the main screening phase, the first reviewer (GB) independently screened titles and abstracts, while the second and third reviewers (VS and PS) cross-verified these results and reviewed the selected studies. Eligible full texts were independently assessed by RM, with verification by SD and JBL. A structured adjudication process was implemented to resolve conflicts, with JBL making the final decision when consensus could not be reached.

Piloted forms were utilized during both the screening and data extraction phases to ensure consistency and accuracy. These forms were tested and refined in the initial stages, standardizing the recording of study characteristics, clinical data, and outcomes.

#### Quality assessment

The quality of included studies was assessed using the Newcastle–Ottawa Scale, which evaluates study selection, comparability, and outcome measures.

#### Statistical analysis

Both quantitative and qualitative data were expressed as percentages. Discordances among variables were resolved by converting them to a standard unit of measurement. A $p$ value $< 0.05$ was considered statistically significant but could not be calculated due to insufficient data. A meta-analysis was initially planned to analyze associations between demographic findings, symptoms, biochemical parameters, and outcomes but was omitted due to insufficient data.

## Results

We identified 760 articles from databases and 178 from pre-print servers. After removing 169 duplicate records, 769 unique records remained. Following title and abstract screening, 650 records were excluded, leaving 119 articles for full-text review. Of these, 84 articles were excluded based on study type (e.g., reviews, correspondence, viewpoints, or commentaries) or failure to meet inclusion criteria. A total of 35 articles were assessed for eligibility, of which 13 were included in the quantitative synthesis, and the remaining 22 were synthesized narratively. This process is illustrated in the PRISMA flow diagram (Fig. 1, Table 1).

Tables 2 and 3 summarize the demographic and clinical features of patients with CNS neuroinflammatory disorders associated with the monkeypox virus and the results of ancillary tests, respectively.

#### Demography and clinical diagnosis

Among the 18 MPXV-infected cases, seven were reported from the USA, three from Nigeria, two from Colombia, and one each from the Democratic Republic of the Congo, Saudi Arabia, India, Spain, the UK, and Sweden (Fig. 2). Of the 18 cases, 12 were men (66.7%), four were women (22.2%), and two (11.1%) did not report age or sex. The mean (median) age was 27.8 (30.0) years, ranging from 28 days to 43 years.

Diagnoses included acute disseminated encephalomyelitis in nine cases (50.0%), encephalitis/

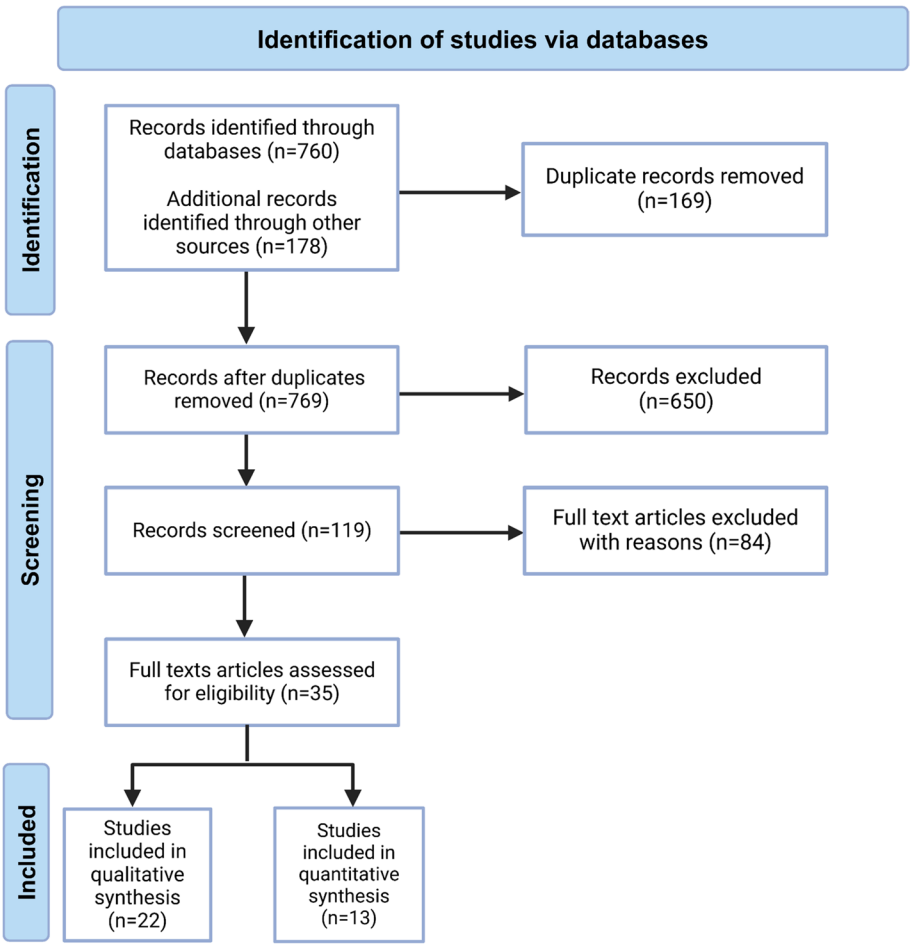


**Fig. 1** PRISMA flow diagram: identification and selection of studies for the systematic review on monkeypox virus-associated neuroinflammatory disorders of the central nervous system

**Table 1** Summary of studies reporting neuroinflammatory disorders of the central nervous system associated with monkeypox virus

| Authors | Country | Article title | Number of cases |
|---|---|---|---|
| Hammad et al. [12] | Saudi Arabia | Unusual neurological complications in a patient with monkeypox: a case report | 1 |
| Money et al. [13] | USA | Monkeypox-associated central nervous system disease: a case series and review | 3 |
| Moore et al. [14] | USA | Transverse myelitis associated with Mpox infection | 1 |
| Cole et al. [15] | UK | Monkeypox encephalitis with transverse myelitis in a female patient | 1 |
| Marín-Medina et al. [16] | Colombia | Encephalomyelitis in a patient with monkeypox: an unusual complication | 1 |
| Pastula et al. [17] | USA | Two cases of monkeypox-associated encephalomyelitis — Colorado and D.C | 2 |
| Rodríguez et al. [18] | Colombia | Acute disseminated encephalomyelitis in a patient with monkeypox: a case report | 1 |
| Karin et al. [19] | Sweden | Monkeypox virus-associated meningoencephalitis diagnosed by detection of intrathecal antibody production | 1 |
| Yadav et al. [20] | India | An imported case of fatal encephalitis associated with Mpox virus infection | 1 |
| Sejvar et al. [21] | USA | Human monkeypox infection: a family cluster in the Midwestern United States | 1 |
| Jezek et al. [22] | Democratic Republic of the Congo | Human monkeypox: clinical features of 282 patients | 1 |
| Ogoina et al. [23] | Nigeria | Clinical course and outcome of human monkeypox in Nigeria | 3 |
| Reuters (Faus) [24] | Spain | Spain reports second monkeypox-related death in Europe | 1 |

**Table 2** Demographic and clinical features of the patients with monkeypox virus-associated central nervous system neuroinflammatory disorders

| Authors | Age/Sex | Systemic symptoms | Neurological manifestations | Comorbidities | Non-neurological complications of illness/hospitalization | Monkeypox virus detection | Cerebrospinal fluid findings | Serum biochemical and serological parameters | Clinical diagnosis | Clinical features of the monkeypox virus | Latency of neurological manifestations | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hammad et al. [12] | 31-year-old male | Fever and disorientation | Paraplegia, urinary retention, dysarthria, right-sided facial weakness, impaired sensation at T11 level | None | None | Quantitative real-time polymerase chain reaction (quantitative real-time polymerase chain reaction) from cutaneous lesion swabs | Elevated protein (68 mg/dL), glucose 71 mg/dL, pleocytosis (25 cells/μL, 68% lymphocytes, 36% polymorphonuclear cells), and negative for other pathogens | Mildly elevated white blood cell count and an elevated erythrocyte sedimentation rate | Encephalomyelitis | Vesiculopapular rash on arms and genitals | 7 days after rash onset | Intravenous immunoglobulin (0.2 g/kg/day for 5 days), brincidofovir (200 mg PO in 2 doses, 8 days apart), and methylprednisolone (1 g/day for 5 days) | Complete neurological recovery within 2 months |
| Money et al. [13] | Male in his 30s (Patient 1) | Fever, malaise, and rash | Headache, left hemiparesis, left-sided numbness, urinary retention, and constipation | Prior known syphilis infection and chronic back pain | Large upper gastrointestinal bleed | Positive polymerase chain reaction from skin lesions | Elevated protein (273 mg/dL), pleocytosis (155 cells/μL, 60% lymphocytes), and negative for monkeypox virus and other pathogens | Positve treponemal serology (negative rapid plasma reagin). Erythrocyte sedimentation rate: 15 mm/h | Acute disseminated encephalomyelitis | Vesiculopustular rash on the face, extremities, and scrotum | 6 days after rash onset | Tecovirimat (600 mg twice daily for 14 days), methylprednisolone, intravenous immunoglobulin, plasmapheresis, and intravenous penicillin | Neurological recovery within 2 months; able to ambulate with a cane at discharge |
| | Male in his 30s (Patient 2) | Fever, myalgia, and rash | Paraplegia, bowel/bladder incontinence, and encephalopathy | Prior treated syphilis | Pulmonary embolism, ventilator-acquired pneumonia, urinary tract infection, and neurogenic fever | Positive polymerase chain reaction from skin lesions | Elevated protein (60 mg/dL), pleocytosis (30 cells/μL, 69% lymphocytes), positive oligoclonal bands (3 bands), and negative for monkeypox virus and other pathogens | Positve treponemal serology (negative rapid plasma reagin). Erythrocyte sedimentation rate: 26 mm/h | Acute disseminated encephalomyelitis | Pustulopapular rash on face, extremities, trunk, and perianal area | 5 days after the onset of the pustulopapular rash | Tecovirimat (oral and IV for 14 days), methylprednisolone, plasmapheresis, and rituximab | Neurological improvement, but gait impairment requiring a cane |
| | Male in his 30s (Patient 3) | Fever and rash | Encephalopathy, agitation, seizure, and nonepileptic truncal clonus | None | None | Indeterminate monkeypox virus testing; epidemiological link to a confirmed case | Elevated protein (63 mg/dL), pleocytosis (20 cells/μL, 94% lymphocytes), and negative for monkeypox virus and other pathogens | Moderate lymphopenia (800 cells/μL) | Acute disseminated encephalomyelitis-like syndrome | Pustulopapular rash on face, extremities, trunk, and perianal area | 4 days after the onset of fever and systemic symptoms | Tecovirimat (IV for 14 days), dexamethasone, acyclovir, and valacyclovir | Complete neurological recovery within one month |

**Table 2** (continued)

| Authors | Age/Sex | Systemic symptoms | Neurological manifestations | Comorbidities | Non-neurological complications of illness/hospitalization | Monkeypox virus detection | Cerebrospinal fluid findings | Serum biochemical and serological parameters | Clinical diagnosis | Clinical features of the monkeypox virus | Latency of neurological manifestations | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Moore et al. [14] | 36-year-old male | Fever, fatigue, abdominal pain, vesicular lesions on upper arms, bilateral groin, and right shin | Rapidly progressive bilateral paraparesis with areflexia, numbness, urinary incontinence, and sensory loss below the T4 level | Well-controlled HIV (low viral load, <40 copies/mL), remote history of syphilis | None | Diagnosis based on characteristic vesicular lesions; monkeypox virus testing in cerebrospinal fluid was not performed due to insufficient sample | White blood cells: 883/μL (83% lymphocytes, 15% monocytes), protein: elevated at 241 mg/dL. Glucose: decreased at 48 mg/dL. One oligoclonal band detected. Myelin basic protein slightly elevated (8.7 μg/L). Negative for bacterial, fungal, and viral pathogens | Positive HIV-1 antibody with undetectable viral load. Positive rapid plasma reagin titer (1:16). Borderline low vitamin B12 (398 pg/mL). Normal folate and other routine serologies | Longitudinally extensive transverse myelitis associated with suspected monkeypox infection | Vesicular lesions on the upper arms, bilateral groin, and right shin | 3 days after systemic symptom onset | Tecovirimat, acyclovir, high-dose IV methylprednisolone (1 g/day for 5 days), intravenous immunoglobulin 0.4 g/kg/day for 5 days, and plasma exchange | Minimal neurological recovery at 5-month follow-up, with persistent spastic paraplegia, bilateral Babinski signs, clonus at both ankles, and T6 sensory level |
| Cole et al. [15] | 35-year-old female | Fever, abdominal pain, groin swelling, painful vesicular vulval lesions, fatigue | Confusion, drowsiness, painless urinary retention, paraparesis progressing to paralysis with areflexia and sensory loss up to the T10 level | Mild gastroesophageal reflux | None | Positive by polymerase chain reaction from genital lesions, throat swabs, and cerebrospinal fluid | Initial lumbar puncture: Mild leukocytosis (16 cells/μL), normal protein (0.4 g/L), normal glucose (3.4 mmol/L). Repeat lumbar puncture: increased lymphocytosis (92 cells/μL, 100% lymphocytes), elevated protein (0.8 g/L). Orthopoxvirus polymerase chain reaction: positive initially, negative in follow-up. No oligoclonal bands | Normal renal and liver function. Negative HIV, hepatitis B, and C serology. Syphilis testing negative | Monkeypox encephalitis with post-infectious longitudinally extensive transverse myelitis | Vesiculopustular rash on vulvovaginal area, limbs, hands, torso, and groin lymphadenopathy with vulval cellulitis | 9 days after systemic symptoms onset | Oral tecovirimat (19 days), intravenous methylprednisolone (1 g/day for 5 days), oral prednisolone (60 mg/day), plasma exchange (7 sessions over 14 days), and a single dose of cidofovir | Significant neurological recovery at 3 months; regained independent walking at follow-up |

**Table 2** (continued)

| Authors | Age/Sex | Systemic symptoms | Neurological manifestations | Comorbidities | Non-neurological complications of illness/hospitalization | Monkeypox virus detection | Cerebrospinal fluid findings | Serum biochemical and serological parameters | Clinical diagnosis | Clinical features of the monkeypox virus | Latency of neurological manifestations | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marín-Medina et al. [16] | 30-year-old male | Fever, cough, fatigue, vesiculopapular rash | Rapidly progressive neurological deterioration, including slurred speech, urinary retention, paraplegia, somnolence, bilateral miosis, bilateral peripheral facial weakness, dysarthria, bilateral Hoffmann sign, and T6 sensory level impairment | History of childhood lymphoproliferative disorder (not active) | Urinary tract infection | Positive polymerase chain reaction from cutaneous lesion swabs, oropharyngeal swabs, and serum. Negative for monkeypox virus DNA in cerebrospinal fluid | Leukocytes: 57 cells/μL (80% mononuclear). Protein: 95 mg/dL. Glucose: 43 mg/dL (serum glucose: 75 mg/dL). Negative for bacterial, fungal, viral pathogens, and other infections | Normal renal and liver function but elevated C-reactive protein levels | Acute disseminated encephalomyelitis associated with monkeypox virus infection | Vesiculopapular rash on lips and genitals | Developed neurological symptoms in the second week of systemic symptoms | High-dose methylprednisolone, intravenous immunoglobulin, and supportive care, including invasive mechanical ventilation and management of complications | Gradual recovery; weaned from mechanical ventilation. After 4 weeks, significant improvement in consciousness, communication, and resolution of cranial nerve symptoms. Residual sensory deficits at T10 |
| Pastula et al. [17] | Male in his 30s (Patient 1) | Fever, chills, malaise, itchy vesiculopustular rash | Left hemiparesis, numbness, urinary retention, and intermittent priapism | Chronic cervical spinal stenosis, presumed not acute, and past syphilis infection | None | Positive polymerase chain reaction for Orthopoxvirus DNA from skin lesions | White blood cells: 155/μL (60% lymphocytes), protein: 273 mg/dL, glucose: 64 mg/dL. Negative for monkeypox virus, herpes simplex virus, varicella-zoster virus, and bacterial cultures. No oligoclonal bands | Negative HIV serology, negative, negative for active syphilis (past syphilis infection noted) | Acute disseminated encephalomyelitis associated with monkeypox virus infection | Diffuse vesiculopustular rash involving face, extremities, and scrotum | 9 days after systemic symptoms onset | Oral tecovirimat, intravenous methylprednisolone and immunoglobulins, intravenous penicillin for prior syphilis, and plasma exchange | Partial improvement in numbness and weakness. Ambulatory with an assistive device at 1-month follow-up |
| | Male in his 30s (Patient 2) | Fever, myalgia, diffuse vesiculopustular rash | Bowel and bladder incontinence, progressive flaccid paraparesis, and altered mental status | Rectal thickening with pelvic lymphadenopathy consistent with proctitis, thought to be related to monkeypox infection | None | Positive polymerase chain reaction for Orthopoxvirus DNA from skin lesions, confirmed as monkeypox virus | White blood cells: 30/μL (89% lymphocytes, 11% monocytes), protein: 60 mg/dL, and glucose: 65 mg/dL. Three oligoclonal bands present. Negative for monkeypox virus, herpes simplex virus, varicella-zoster virus, and bacterial cultures | Negative HIV serology | Acute disseminated encephalomyelitis associated with monkeypox | Diffuse vesiculopustular rash involving face, extremities, trunk, and perianal area | 5 days after systemic symptoms onset | Oral and intravenous tecovirimat, intravenous methylprednisolone and immunoglobulins, plasma exchange, and intravenous rituximab for maintenance immunosuppression | Substantial improvement, ambulating with an assistive device after discharge to inpatient rehabilitation |

**Table 2** (continued)

| Authors | Age/Sex | Systemic symptoms | Neurological manifestations | Comorbidities | Non-neurological complications of illness/hospitalization | Monkeypox virus detection | Cerebrospinal fluid findings | Serum biochemical and serological parameters | Clinical diagnosis | Clinical features of the monkeypox virus | Latency of neurological manifestations | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rodríguez et al. [18] | 30-year-old male | Asthenia, adynamia, odynophagia, and pustular lesions | Progressive paraparesis, urinary retention, dysarthria, altered mental status ranging from lethargy to drowsiness | History of lymphoid hematological neoplasia at age 5 (in remission, no active disease at presentation) | None | Confirmed by polymerase chain reaction from pustular lesions | Pleocytosis and hyperproteinorrachia with negative gram stain | Normal renal function, electrolytes, and inflammatory markers except elevated C-reactive protein. HIV and hepatitis serologies were negative | Acute disseminated encephalomyelitis associated with monkeypox infection | Pustular lesions on the lower lip, genital region, and suprapubic area | 2 days after systemic symptoms onset | Not reported | Significant improvement by the second week; full recovery of consciousness, urinary retention, dysarthria, and lower limb strength noted by discharge |
| Karin et al. [19] | 37-year-old male | Painful genital and oral ulcers, mild vesiculopustular lesions on lower limbs and trunk, fever, sore throat, headache, and fatigue | Confusion, psychomotor deceleration, progressive disorientation, localized pain response, and a decline in Glasgow Coma Scale from 14/15 to 9/15, with no focal neurological deficits | History of primary syphilis, treated five months prior; regular pre-exposure prophylaxis for HIV | | Positive polymerase chain reaction from genital and oral lesions. Negative polymerase chain reaction for monkeypox virus in cerebrospinal fluid. Intrathecal production of monkeypox virus antibodies confirmed | Day 1: Mononuclear pleocytosis (22 cells/μL), protein (59 mg/dL), normal glucose (4.0 mmol/L). Day 3: Increased mononuclear cells (66 cells/μL), protein (61 mg/dL), and normal glucose (4.1 mmol/L). Intrathecal antibody production detected; negative for herpes simplex virus, varicella-zoster virus, cytomegalovirus, and other pathogens | Elevated C-reactive protein and mildly elevated liver enzymes. Normal renal function | Monkeypox-associated meningoencephalitis confirmed by intrathecal antibody production | Vesiculopustular rash on genital area, trunk, and lower extremities, associated with ulcers | 12 days from onset of systemic symptoms to confusion | Empirical acyclovir (discontinued after negative herpes simplex virus polymerase chain reaction) and supportive care; no immunomodulatory treatment was administered. | Rapid improvement; fully oriented and functional by day 4 of admission. Complete recovery confirmed at 45-day follow-up |
| Yadav et al. [20] | 22-year-old male | Fever, headache, painful right inguinal lymphadenopathy with abscess, and fatigue | Generalized tonic-clonic seizure and Glasgow Coma Scale score of 7 | None | Acute kidney injury, coagulopathy, elevated intracranial pressure, and brainstem dysfunction | Positive by quantitative real-time-polymerase chain reaction from oropharyngeal and nasopharyngeal swabs | Polymorphonuclear pleocytosis (75 cells/μL; 80% lymphocytes, 20% neutrophils), elevated protein (84.3 mg/dL), normal glucose (58 mg/dL), elevated adenosine deaminase, and lactate dehydrogenase | Elevated erythrocyte sedimentation rate (42 mm/hr), D-dimer (1240 ng/mL), ferritin (299.3 mg/L), C-reactive protein (12.9 mg/dL), and lactate dehydrogenase (584 IU/L). Elevated blood urea (29 mg/dL) and serum creatinine (2.30 mg/dL). Normal liver function. | Acute meningoencephalitis likely caused by monkeypox virus (direct or autoimmune mechanism suspected) | Right inguinal lymphadenopathy with abscess and a doubtful healed scrotal lesion | 11 days | Empirical antibiotics, antivirals (acyclovir), anti-tubercular drugs, mechanical ventilation, and supportive care | Deceased due to brainstem dysfunction |

**Table 2** (continued)

| Authors | Age/Sex | Systemic symptoms | Neurological manifestations | Comorbidities | Non-neurological complications of illness/hospitalization | Monkeypox virus detection | Cerebrospinal fluid findings | Serum biochemical and serological parameters | Clinical diagnosis | Clinical features of the monkeypox virus | Latency of neurological manifestations | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sejvar et al. [21] | 6-year-old female | Fever, sore throat, malaise, anorexia, headache | Somnolence, acute unresponsiveness, pupillary dilation, muscle rigidity, sustained clonus, and bilateral Babinski signs | None | None | Positive by polymerase chain reaction and viral culture from skin lesions and Orthopoxvirus IgM detected in cerebrospinal fluid | White blood cells: 21 cells/$mm^3$ (60% polymorphonuclear cells, 34% lymphocytes), protein 32 mg/dL, and glucose 94 mg/dL | Normal electrolytes, liver function, and metabolic panels | Monkeypox-associated encephalitis | Vesiculopustular rash evolving uniformly, predominantly on extremities, palms, soles, and face | 6 days after systemic symptom onset | Empiric intravenous ceftriaxone, acyclovir, phenobarbital, midazolam, and supportive care with mechanical ventilation | Improved encephalopathy, with resolution of fever and recovery of neurological function. Discharged 16 days after admission with complete neurological recovery noted at follow-up. |
| Jezek et al. [22] | 3-year-old female | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Encephalitis | Not reported | Not reported | Not reported | Deceased |
| Ogoina et al. [23] | 43-year-old male | Not reported | Seizures | HIV-1 infection | Not reported | Not reported | Not reported | Not reported | Encephalitis | Not reported | Not reported | Not reported | Deceased |
| | 28-day-old female | Not reported | Generalized seizures | Not reported | Bronchopneumonia | Not reported | Not reported | Not reported | Encephalitis | Not reported | Not reported | Not reported | Deceased |
| | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Encephalitis | Not reported | Not reported | Not reported | Not reported |
| Reuters (Faus) [24] | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Encephalitis | Not reported | Not reported | Not reported | Deceased |

**Table 3** Summary of the studies reporting neuroimaging findings, electroencephalogram, and autoimmune panels associated with MPXV-associated neuroinflammatory disorders

| Authors | Spinal cord imaging | Brain magnetic resonance imaging | Electroencephalography Parameters | Autoimmune Panel | |
|---|---|---|---|---|---|
| | | | | Cerebrospinal fluid | Serum |
| Hammad et al. [12] | Long-segment hyperintense signals on T2-weighted and FLAIR sequences observed in the cervical and upper thoracic spinal cord, occupying more than two-thirds of the cross-sectional area. Mild cord swelling in the upper cervical spine. No enhancement observed in the spinal cord, but increased meningeal enhancement along the anterior and posterior margins. | Multiple hyperintense signals in the cortical and subcortical regions of both hemispheres on T2-weighted and FLAIR sequences. Hyperintense signals observed in the basal ganglia, thalamus, medial temporal lobe, insular cortex, and brainstem. Subtle enhancement noted in the brainstem, with no other significant findings. | Not Reported | Not Reported | Not reported |
| Money et al. [13] | | | | | |
| Patient 1 | Multifocal, longitudinally extensive, partially enhancing central thoracic lesions with a gray matter lesion in the conus medullaris | Partially enhancing T2/FLAIR hyperintense subcortical lesion in the right frontal lobe, with additional lesions in the bilateral medial thalami, basal ganglia, splenium, and pons. | Generalized rhythmic delta activity and slowing | Not reported | Negative for myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies |
| Patient 2 | Multifocal, partially enhancing T2 hyperintense lesions in the cervical and thoracic spine with central cord and dorsal column involvement | Ill-defined T2/FLAIR hyperintensities in the cerebellum, pons, and medulla, with persistent DWI hyperintensities | Not Reported | Not reported | Positive for anti-smooth muscle antibodies, negative for aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies |
| Patient 3 | No abnormalities detected in cervical or thoracic spinal imaging. | Restricted diffusion in the central and lateral thalami and posterior globus pallidi, with subtle T2/FLAIR hyperintensity; no parenchymal or leptomeningeal enhancement. | Generalized rhythmic delta activity and generalized bifrontal slowing. | Not reported | Not reported |
| Moore et al. [14] | Longitudinally extensive, non-enhancing T2/FLAIR hyperintense lesion in the thoracic spinal cord, spanning T1 to T10 vertebral levels—slight swelling of the cord in the same distribution.<br>Lesion was central, predominantly involving gray matter | Multiple discrete, non-enhancing T2/FLAIR hyperintensities. Lesions located in the left external capsule, central pons, left cerebellar white matter, and right middle cerebellar peduncle | Not Reported | Negative | Negative |

**Table 3** (continued)

| Authors | Spinal cord imaging | Brain magnetic resonance imaging | Electroencephalography Parameters | Autoimmune Panel | |
|---|---|---|---|---|---|
| | | | | Cerebrospinal fluid | Serum |
| Cole et al. [15] | Longitudinally extensive transverse myelitis. T2 hyperintense signal along the entire spinal cord with both central gray and peripheral white matter involvement. Cord swelling observed in the cervicothoracic and lumbar regions. Post-contrast enhancement in the cauda equina nerve roots and patchy enhancement in the cervical spine | Diffuse T2 hyperintensities throughout the cerebral white matter. Hyperintensities in both thalami, middle cerebellar peduncle, and brainstem. New lesions in the posterior limb of the left internal capsule and splenium of the corpus callosum. Cortical swelling with early uncal herniation and brainstem mass effect | Not Reported | Negative for aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies, paraneoplastic autoantibodies, and autoantibodies to glial fibrillary acidic protein | Negative for aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies, antinuclear antibodies, extractable nuclear antigens, paraneoplastic autoantibodies, and autoantibodies to glial fibrillary acidic protein |
| Marín-Medina et al. [16] | T2/STIR hyper-intense longitudinally extensive transverse myelitis comprising levels T1 to T12, with no enhancement or compression | Extensive T2/FLAIR hyperintensities were observed, primarily affecting the white matter of the brain hemispheres, as well as the basal ganglia, anterior thalamus, internal capsules, frontal medial cortex, cerebral peduncles, and the entire pons. Some lesions exhibited restricted diffusion with mild contrast enhancement and no evidence of compression | Not Reported | Not reported | Negative aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies |
| Pastula et al. [17] Patient 1 | Multifocal, longitudinally extensive, partially enhancing lesions in the central thoracic spinal cord. Gray matter involvement in the conus medullaris. Chronic cervical spinal stenosis causing partial cord compression (presumed non-acute) | Partially enhancing lesions in the frontal lobes (consistent with demyelination). Non-enhancing lesions in the bilateral basal ganglia, medial thalami, splenium, and pons | Not reported | Not reported | Negative aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies |
| Patient 2 | Multifocal, partially enhancing lesions in the central cervical and thoracic spinal cord. Gray matter involvement | Non-enhancing T2/FLAIR hyperintensities in the pons, cerebellum, and medulla. No restricted diffusion noted | Not reported | Negative aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies | Negative aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies |

**Table 3** (continued)

| Authors | Spinal cord imaging | Brain magnetic resonance imaging | Electroencephalography Parameters | Autoimmune Panel | |
|---|---|---|---|---|---|
| | | | | Cerebrospinal fluid | Serum |
| Rodríguez et al. [18] | Longitudinally extensive intramedullary T2 hyperintensity from T1 to T8 and T11 suggestive of inflammation or demyelination | T2/FLAIR hyperintensities in the anterior right thalamus, bilateral lentiform nuclei, posterior insular regions, left frontal parasagittal area, pons, and midbrain, with no restricted diffusion or gadolinium enhancement | Not reported | Negative myelin oligodendrocyte glycoprotein antibodies and paraneoplastic antibodies (anti-Hu, Yo, Ri, Ma) | Not reported |
| Karin et al. [19] | Not reported | Bilateral symmetrical restricted diffusion in the cingulate gyrus, insula, and cortical regions | Generalized slow waves without epileptiform activity | Negative | Negative |
| Yadav et al. [20] | Not reported | Diffuse cerebral edema. Altered signal intensity with FLAIR hyperintensity and mild restricted diffusion. Lesions observed in bilateral cerebral cortical and subcortical regions, bilateral caudate nucleus, putamen, and posterior genu of the corpus callosum. | Generalized cerebral dysfunction | not reported | Not reported |
| Sejvar et al. [21] | Not reported | Diffuse cortical, thalamic, and brainstem edema, meningeal enhancement, and left thalamic and right parietal signal abnormality | Generalized slowing, consistent with diffuse cerebral dysfunction | Not reported | Not reported |
| Jezek et al [22] | Not reported | Not reported | Not reported | Not reported | Not reported |
| Ogoina et al. [23] | Not reported | Not reported | Not reported | Not reported | Not reported |
| Reuters (Faus) [24] | Not reported | Not reported | Not reported | Not reported | Not reported |

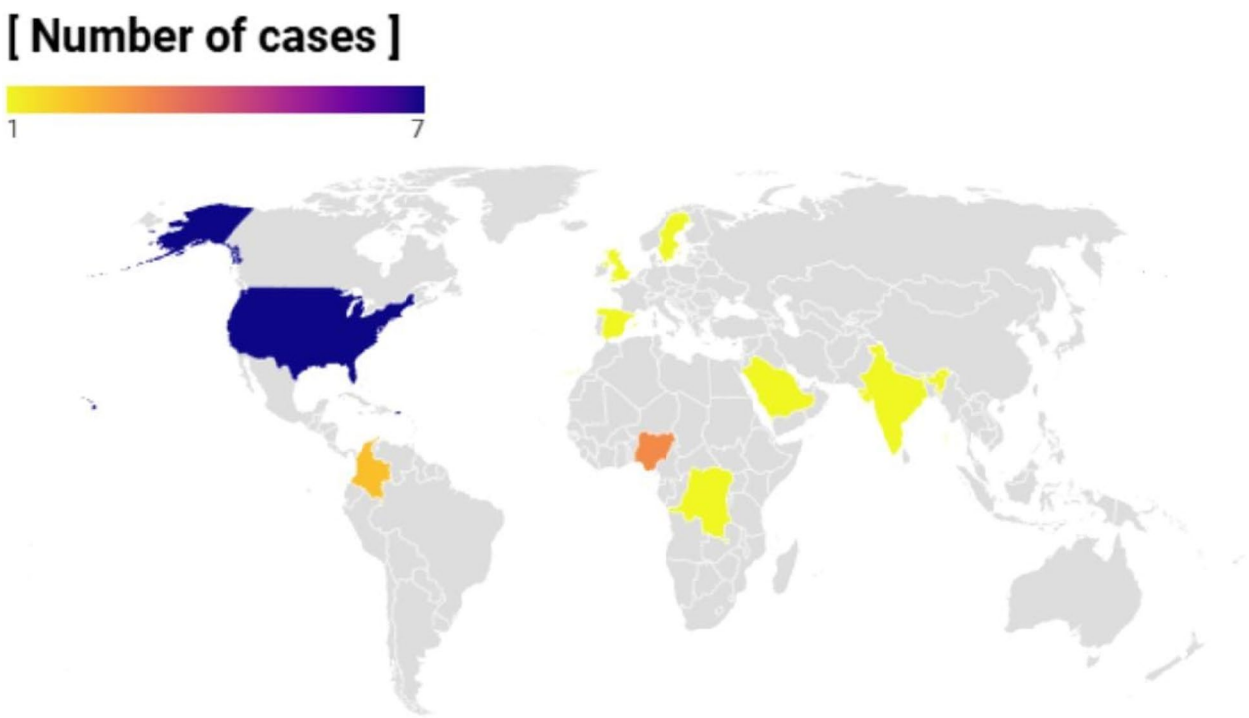


**Fig. 2** Global distribution of reported cases of neuroinflammatory disorders of the central nervous system associated with monkeypox virus

meningoencephalitis in seven cases (38.9%), isolated transverse myelitis in one case (5.6%), and transverse myelitis with encephalitis in one case (5.6%).

#### Systemic symptoms, comorbidities, and non-neurological complications of illness/hospitalization

Systemic manifestations were described in 13 cases (72.2%). Of these, fever was the most common manifestation, occurring in 12 cases (92.3%), followed by fatigue in 5 cases (38.5%) and malaise in 3 cases (23.1%). Rash, in various forms, was described in 12 cases (92.3%). Lymphadenopathy, sore throat, and disorientation were noted in individual cases, showcasing a broad range of presentations (Table 2).

The presence or absence of comorbidities was reported in 13 cases (72.2%), with syphilis (4 cases), human immunodeficiency virus (HIV) (2 cases), and lymphoid hematological neoplasia/lymphoproliferative disorders (2 cases) being the most common. Non-neurological complications of the illness and hospitalization included pulmonary embolism, ventilator-associated pneumonia, acute kidney injury, coagulopathy, and gastrointestinal bleeding, among others (Table 2).

#### Monkeypox virus detection, skin lesion distribution, and characteristics

MPXV detection was reported in 13 of 18 cases (72.2%), primarily using quantitative real-time polymerase chain reaction (qRT-PCR) from various biological specimens. Of these, the most common diagnostic method was qRT-PCR from cutaneous lesion swabs, reported in 10 cases (76.9%). Additional specimen types included oropharyngeal and nasopharyngeal swabs, genital and oral lesions, and serum. Cerebrospinal fluid (CSF) MPXV detection was confirmed in one case [15]. Conversely, in another case, intrathecal MPXV antibody production was detected despite negative CSF qRT-PCR [19]. Five cases (27.8%) did not explicitly report MPXV detection methods. One case had an indeterminate MPXV qRT-PCR result from skin lesions, with equivocal MPXV IgM and negative MPXV IgG (patient 3 from Money et al. [13]) (Table 2).

The presence or absence of skin lesion was reported in 13 cases, and the distribution varied among cases, with most patients exhibiting vesiculopustular rashes across multiple anatomical sites. The most commonly affected areas were the genital/perianal region in 10 cases (76.9%), extremities in 9 cases (69.2%), the face in 8 cases (61.5%), and the trunk in 6 cases (46.1%). In one case (7.7%), there were no active skin lesions [20] (Table 2).

#### Neurological manifestations

Neurological manifestations were reported in 15 of the 18 cases, demonstrating a broad range of clinical presentations. Of these, paraplegia or paraparesis was the most frequent finding, affecting 7 cases( 46.7%), often

accompanied by urinary retention (6 cases, (40%) and sensory deficits. Encephalopathy with confusion, agitation, or altered consciousness was observed in 7 cases (46.7%), while seizures occurred in 4 cases (26.7%) (Table 2).

The latency period between the onset of systemic symptoms and the development of neurological manifestations was reported in 13 of the 15 cases with neurological symptoms (86.7%). The mean (median) latency was 6.2 (6.0) days, ranging from 2 to 12 days (Table 2). In most cases, neurological symptoms emerged within the first week of systemic illness, indicating rapid progression.

#### Biochemical and laboratory parameters

Biochemical and laboratory parameters in serum and CSF were reported in 13 of the 18 cases (72.2%). Serum inflammatory markers were elevated in several cases. Erythrocyte sedimentation rate was increased in 4 cases, and C-reactive protein in 3 cases. Additional findings included elevated levels of ferritin, lactate dehydrogenase, and D-dimer, indicating systemic inflammation and possible coagulopathy. Renal and liver function tests were normal in most cases, except in those complicated by acute kidney injury or multi-organ dysfunction (Table 2). Cerebrospinal fluid (CSF) analysis was performed in 13 cases (72.2%), all of which exhibited pleocytosis (100%) , with white blood cell counts ranging from 16 to 883 cells/μL and a predominance of lymphocytes. Elevated protein levels were observed in 12 of 13 cases (92.3%), while glucose levels were generally within the normal range, with mild hypoglycorrhachia reported in isolated cases (Table 2).

#### Electroencephalography results

Electroencephalography findings were reported in 5 cases (27.7%), and all of them demonstrated abnormalities. The predominant findings included generalized slowing and rhythmic delta activity, indicative of diffuse cortical dysfunction. These patterns were consistent with encephalopathic changes (Table 3).

#### Neuroimaging findings

Neuroimaging findings were reported in 10 of the 18 cases (55.5%) and revealed widespread CNS involvement in MPXV-associated neuroinflammatory disorders. Magnetic resonance imaging was the primary modality used and demonstrated characteristic abnormalities across both the brain and spinal cord.

Spinal imaging findings were notable for longitudinally extensive transverse myelitis in several cases, characterized by hyperintense T2 signals spanning multiple vertebral segments and affecting both the central gray and peripheral white matter. Associated findings included spinal cord swelling and patchy contrast enhancement.

Brain imaging abnormalities were predominantly located in the basal ganglia, thalamus, corpus callosum, and brainstem, with hyperintense signals on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. These lesions often reflected diffuse cortical and subcortical involvement, consistent with acute disseminated encephalomyelitis or encephalitis. Specific cases exhibited focal contrast enhancement, suggesting blood–brain barrier disruption. Cerebellar and middle cerebellar peduncle involvement were also documented in isolated instances (Table 3).

#### Treatment and outcome

Treatment details were reported in 12 of the 18 cases (66.7%), reflecting varied approaches to managing MPXV-associated CNS neuroinflammatory disorders. Antiviral therapy was a cornerstone of treatment, with tecovirimat being the most commonly used antiviral, administered in 7 cases (58.3%). Other antivirals, including acyclovir, brincidofovir, and cidofovir, were used in specific cases.

Immunomodulatory therapies were widely employed, with intravenous methylprednisolone frequently (8 cases, 66.7%) followed by oral corticosteroids. Intravenous immunoglobulin and plasmapheresis were used in several cases, typically for patients with severe disease or poor initial response to other treatments. Rituximab was used in two cases for maintenance immunosuppression in acute disseminated encephalomyelitis or similar conditions.

Supportive care was critical in severe cases, with mechanical ventilation provided for patients with respiratory failure or encephalopathy requiring intubation. Management of complications, such as ventilator-associated pneumonia, pulmonary embolism, and gastrointestinal bleeding, was also integral to the overall treatment strategy.

Outcomes were reported in 17 of the 18 cases (94.4%). Of these five patients (29.4%) achieved complete neurological recovery within 1 to 3 months of treatment, demonstrating the potential for favorable outcomes with early and aggressive intervention. Partial recovery was documented in 7 cases (41.2%), with neurological deficits ranging from mild residual symptoms to persistent impairments requiring assistive devices. Five patients died, representing 29.4% of the group. Brainstem dysfunction was documented as the cause of one death, while the causes of the other four deaths remained unreported.

## Discussion

This systematic review highlights 18 cases of MPXV-associated CNS neuroinflammatory disorders, revealing the virus's capacity to cause severe and multifocal

CNS involvement. The spectrum of diagnoses—including acute disseminated encephalomyelitis in nine cases (50.0%), encephalitis/meningoencephalitis in seven cases (38.9%), isolated transverse myelitis in one case (5.6%) and transverse myelitis with encephalitis in one case (5.6%)—emphasizes the diverse pathogenic mechanisms underlying these complications. The latency between systemic and neurological symptom onset, averaging 6.2 days, underscores the rapid progression in many cases, necessitating timely clinical vigilance.

Emerging evidence suggests that MPXV induces a robust immunological response characterized by cytokine dysregulation and immune cell activation, which may drive neuroinflammatory manifestations [25]. Elevated levels of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, persist even after clinical recovery, indicating a sustained inflammatory state that could exacerbate CNS involvement [25]. Immune dysregulation, marked by CD4 + T cell depletion and CD8 + T cell expansion, may contribute to direct viral neuroinvasion while simultaneously promoting immune-mediated CNS injury [25].

MPXV also exhibits neuroinvasive potential, accessing the CNS through pathways such as the olfactory epithelium and infected monocytes/macrophages [26]. Its ability to bypass the blood–brain barrier allows for direct infection of neural tissues, with the detection of MPXV in CSF further supporting its role in CNS inflammation and neurological dysfunction [15, 26]. These pathological mechanisms likely involve a synergistic interplay between direct viral invasion and immune-mediated processes, leading to neurological complications in affected individuals.

Recent findings by Miranzadeh Mahabadi et al. [27] provide additional insights into MPXV pathogenesis, elucidating specific cellular receptor interactions and mechanisms in human astrocytes. The study demonstrated that astrocytes, identified as the most permissive cell type for MPXV infection, actively support viral replication and trigger gasdermin B cleavage and pyroptosis, a form of inflammatory cell death. Proteomic analyses revealed the presence of over 125 MPXV-encoded proteins in infected astrocytes, signifying robust and specific interactions between MPXV and these glial cells. Microglia also exhibited susceptibility to MPXV infection, whereas neuronal infection remained minimal, highlighting a distinct tropism for glial cells. These findings further support the hypothesis that glial dysfunction and inflammatory responses contribute significantly to MPXV associated neuropathology, reinforcing the interplay between viral effects and secondary immune mediated damage in CNS involvement [27].

Diagnostic evaluation remains a cornerstone in managing MPXV-associated neuroinflammatory disorders. Molecular techniques, particularly qRT-PCR, are critical for confirming MPXV infection in clinical specimens, while CSF analysis and MRI are indispensable for assessing CNS involvement. Magnetic resonance imaging findings frequently demonstrated characteristic hyperintense lesions in the brain and spinal cord, consistent with demyelinating or inflammatory processes such as acute disseminated encephalomyelitis or transverse myelitis. In cases where direct viral detection was elusive, evidence of intrathecal antibody production has proven valuable for confirming CNS infection [19].

Management strategies for MPXV-associated neuroinflammatory disorders face significant challenges due to the absence of standardized treatment protocols. Antiviral therapies, particularly tecovirimat, were the cornerstone of the treatment in over half of the cases with reported treatments, though outcomes varied significantly [13–15, 17]. Adjunctive immunomodulatory therapies, including corticosteroids, intravenous immunoglobulin, and plasmapheresis, were often employed in cases with suspected immune-mediated pathology. The variable outcomes observed—from complete recovery in 29.4% of cases to mortality in 29.4%—highlight the need for early diagnosis and tailored therapeutic strategies. Severe cases often required intensive supportive care, including mechanical ventilation for encephalopathy or respiratory failure [16, 20, 21].

The emergence of MPXV-associated neuroinflammatory disorders has profound implications for public health and clinical practice. Enhanced surveillance is essential to determine the true incidence and spectrum of these complications, particularly in regions with endemic or emerging outbreaks. Clinicians should maintain a high index of suspicion for CNS involvement in MPXV patients presenting with new-onset neurological symptoms, especially during active outbreaks. Vaccine strategies against MPXV should also consider the historical precedent of neurological complications associated with orthopoxvirus vaccines [28–31], necessitating careful monitoring for adverse events.

Future research should prioritize longitudinal cohort studies to accurately assess the incidence, risk factors, and outcomes of MPXV-associated CNS complications. Mechanistic studies are critical to delineating the pathways of MPXV neuroinvasion and immune-mediated CNS damage. Additionally, clinical trials evaluating antiviral and immunomodulatory therapies are imperative to establish evidence-based treatment guidelines. Particular attention should be given to understanding clade-specific differences in neurovirulence and their implications for clinical management and vaccine strategies. We

recognize several limitations of this systematic review. The small number of reported cases ($N$=18) limits the generalizability of our findings, and publication bias may have contributed to an over representation of severe or atypical cases. Additionally, the absence of standardized diagnostic criteria and reporting methods for MPXV-associated neurological complications complicates case comparisons. As a systematic review, we relied on the diagnostic classification provided by the authors of the included studies, acknowledging the potential variability in definitions across sources and the critical need for standardized criteria. Although a meta-analysis was not feasible due to data heterogeneity, we emphasize the rigor and robustness of our systematic review process.

## Conclusions

This systematic review highlights the potential for MPXV to cause severe neuroinflammatory disorders of the CNS, characterized by significant variability in the clinical presentation and outcomes. Although rare, these conditions can lead to serious complications, the necessitating heightened clinical vigilance, advanced diagnostic approaches, and targeted therapeutic strategies. The evolving global burden of MPXV, including outbreaks in the Democratic Republic of the Congo and beyond, underscores the need for standardize diagnostic criteria, increased awareness and international collaboration. Further research is essential to elucidate the mechanisms underlying MPXV neurovirulence and to develop effective treatments for these life-threatening neurological complications.

### Abbreviations

| | |
|---|---|
| CNS | Central nervous system |
| CSF | Cerebrospinal fluid |
| FLAIR | Fluid-attenuated inversion recovery |
| HIV | Human immunodeficiency virus |
| MPXV | Monkeypox virus |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| qRT-PCR | Quantitative real-time polymerase chain reaction |

### Authors' contributions

Shramana Deb collaborated on (1) the conception, organization, and execution of the research project, (2) the statistical analysis design, and (3) the writing of the first draft of the manuscript. Ritwick Mondal collaborated on (1) the conception, organization, and execution of the research project, (2) the statistical analysis design, and (3) the writing of the first draft of the manuscript. Purbita Sen collaborated on (1) data extraction, (2) data organization, and (3) coordination of literature searches from different databases. Dipanjan Chowdhury collaborated on (1) data extraction, (2) data organization, and (3) coordination of literature searches from different databases. Shramana Sarkar collaborated on (1) data extraction, (2) data organization, and (3) coordination of literature searches from different databases. Granthik Banerjee collaborated on (1) data extraction, (2) data organization, and (3) coordination of literature searches from different databases. Vramanti Sarkar collaborated on (1) data extraction, (2) data organization, and (3) coordination of literature searches from different databases. Anjan Chowdhury collaborated on (1) data extraction, (2) data organization, (3) literature search strategy from different databases, and (4) statistical analysis. Julián Benito-León collaborated on (1) the conception, organization, and execution of the research project and (2) the writing of the first draft of the manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

As this study is a systematic review of published literature, no ethics approval or patient consent was required.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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