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EBOLA HEMORRHAGIC FEVER ENCEPHALITIS: EPIDEMIOLOGY, NEUROBIOLOGY, NEUROPATHOLOGY, CLINICAL MANIFESTATIONS, DIAGNOSIS, MANAGEMENT, AND FUTURE DIRECTIONS—DESCRIPTIVE REVIEW

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ABSTRACT

Background: Ebola virus disease (EVD) is a severe zoonotic infection caused by members of the family *Filoviridae* and remains one of the most lethal viral hemorrhagic fevers affecting humans. Although historically recognized for its systemic manifestations, increasing evidence demonstrates significant neurological involvement during both acute infection and long-term survivorship. Ebola hemorrhagic fever encephalitis has emerged as an important contributor to morbidity, mortality, and chronic disability among affected individuals. **Objective:** This descriptive review synthesizes current evidence regarding the epidemiology, virology, neurobiology, neuropathology, clinical manifestations, diagnosis, management, prognosis, and future directions of Ebola hemorrhagic fever encephalitis. **Methods:** A comprehensive literature review was conducted using PubMed/MEDLINE, Web of Science, and Google Scholar databases covering publications from 2010 through 2026. Additional landmark studies published before 2010 were included when relevant. Articles addressing neurological manifestations, central nervous system invasion, neuroimmunology, neuropathology, diagnosis, treatment, survivor outcomes, and public health implications were reviewed and synthesized narratively. **Results:** Accumulating evidence indicates that Ebola virus possesses significant neuroinvasive potential. Neurological manifestations range from headache, encephalopathy, seizures, and meningoencephalitis during acute infection to persistent cognitive dysfunction, neuropsychiatric disorders, movement abnormalities, neuropathic pain, visual impairment, and chronic post-Ebola neurological syndrome among survivors. Current evidence supports a multifactorial pathogenesis involving direct viral neuroinvasion, blood-brain barrier disruption, endothelial dysfunction, neuroinflammation, microglial activation, cerebrovascular injury, and persistent viral reservoirs within immune-privileged compartments. Advances in molecular diagnostics and monoclonal antibody therapies have improved survival; however, substantial neurological morbidity persists among survivors. **Conclusions:** Ebola hemorrhagic fever encephalitis represents a major but historically underrecognized component of Ebola virus disease. Recognition of its neuroinfectious and neuroinflammatory characteristics has fundamentally altered understanding of Ebola pathogenesis and survivorship. Future efforts should prioritize early diagnosis, neurological surveillance, biomarker development, rehabilitation services, and investigation of persistent viral reservoirs to reduce long-term neurological disability and improve outcomes among survivors.

KEYWORDS: Ebola virus disease; Ebola hemorrhagic fever; encephalitis; neuroinflammation; neuropathology; viral persistence; central nervous system; neurovirology; survivor syndrome; neuroinfectious disease.

INTRODUCTION

Ebola virus disease (EVD) is a severe zoonotic infection caused by members of the genus *Orthoebolavirus* within the family *Filoviridae*. Since its initial recognition during simultaneous outbreaks in Zaire and Sudan in 1976, EVD has emerged as one of the most lethal viral hemorrhagic fevers known to affect humans, with reported case fatality rates ranging from approximately 25% to 90% depending on viral species, outbreak characteristics, healthcare infrastructure, and availability of supportive care.[1,2] The unprecedented West African epidemic of 2014–2016 transformed global understanding of Ebola virus disease by demonstrating its capacity for sustained urban transmission and by generating an unprecedented number of survivors who could be followed longitudinally to evaluate long-term sequelae.[3,4]

Historically, Ebola virus disease was viewed primarily as an acute systemic illness characterized by fever, gastrointestinal manifestations, coagulopathy, endothelial dysfunction, shock, and multiorgan failure.[2,5] Neurological manifestations received relatively little attention during earlier outbreaks because the overwhelming mortality often limited detailed neurological assessment. Moreover, the scarcity of neuroimaging facilities, cerebrospinal fluid analysis, neuropathological studies, and specialist neurological services in outbreak regions contributed to a substantial underappreciation of central nervous system involvement.[6,7]

Over the past decade, however, accumulating clinical, radiological, molecular, and pathological evidence has fundamentally altered this perspective. Increasing numbers of survivors have been shown to develop acute neurological complications, including encephalopathy, encephalitis, seizures, meningoencephalitis, cranial neuropathies, movement disorders, and stroke-like syndromes, as well as chronic neurocognitive and neuropsychiatric sequelae that may persist for years after apparent recovery.[8–12] These findings indicate that the nervous system represents an important target of Ebola virus infection and that neurological injury contributes substantially to both acute morbidity and long-term disability among survivors.

The recognition of viral persistence within immune-privileged anatomical compartments has further revolutionized understanding of Ebola neuropathogenesis. Several landmark investigations have demonstrated the presence of Ebola viral RNA within cerebrospinal fluid months after clearance from peripheral blood, accompanied by relapsing meningoencephalitis and severe neurological deterioration.[8,13] Such observations challenge traditional assumptions regarding viral eradication following recovery and suggest that the central nervous system may serve as a reservoir capable of sustaining prolonged infection and delayed disease recurrence.

The concept of Ebola hemorrhagic fever encephalitis has consequently emerged as an increasingly important area of investigation within neuroinfectious disease research. Contemporary evidence suggests that neurological injury results from a complex interplay between direct viral neuroinvasion, endothelial dysfunction, blood-brain barrier disruption, neuroinflammation, cytokine-mediated toxicity, cerebrovascular injury, and persistent immune activation.[14–18] Rather than representing a single pathological process, Ebola-associated neurological disease appears to encompass a spectrum of acute and chronic CNS disorders arising through multiple overlapping mechanisms.

Experimental studies have demonstrated that Ebola virus exhibits the capacity to infect monocytes, macrophages, dendritic cells, endothelial cells, astrocytes, microglia, and potentially other neural cell populations.[19–22] Viral dissemination through infected leukocytes, often described as a "Trojan horse" mechanism, may facilitate transport across vascular barriers and contribute to CNS invasion. Simultaneously, systemic cytokine storms characterized by

excessive production of tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, interferon-gamma, and numerous chemokines promote endothelial injury and compromise blood-brain barrier integrity, thereby facilitating entry of viral particles and inflammatory mediators into neural tissues.[23–26]

The neuropathological consequences of these processes are increasingly recognized. Available human and experimental data have identified cerebral edema, meningeal inflammation, microglial activation, reactive astrogliosis, neuronal degeneration, microvascular thrombosis, perivascular inflammatory infiltrates, white matter injury, and multifocal hemorrhage among affected individuals.[17,27–29] These pathological findings suggest that Ebola encephalitis shares features with both viral encephalitides and inflammatory cerebrovascular disorders, thereby accounting for the diverse clinical manifestations observed among survivors.

The neurological burden of Ebola virus disease extends well beyond the acute phase of infection. Large survivor cohorts from Liberia, Sierra Leone, Guinea, and the Democratic Republic of Congo have documented persistent headaches, cognitive dysfunction, memory impairment, depression, anxiety, tremor, neuropathic pain, sleep disturbances, visual impairment, cranial neuropathies, and reduced quality of life years after recovery.[10–12,30–33] Such findings have prompted increasing recognition of post-Ebola neurological syndrome as a significant contributor to long-term disability and public health burden in affected populations.

Importantly, these neurological complications carry implications that extend beyond individual patients. Survivors experiencing cognitive impairment may encounter difficulties returning to employment, education, and community life. Psychiatric disorders and chronic neurological symptoms may further exacerbate social stigma, economic hardship, and healthcare utilization. Consequently, the long-term neurological consequences of Ebola virus disease have become an important component of outbreak recovery planning and global health policy.[31–34]

Despite considerable advances in understanding Ebola neuropathogenesis, substantial gaps in knowledge remain. The true incidence of encephalitis is unknown, standardized diagnostic criteria are lacking, neuropathological data remain limited, and the mechanisms underlying persistent viral reservoirs continue to be actively investigated. Furthermore, relatively little is known regarding the neurological manifestations associated with non-Zaire ebolavirus species, pediatric populations, or the long-term effects of emerging antiviral therapies on neurological outcomes.[13,17,35]

This descriptive review synthesizes current evidence regarding Ebola hemorrhagic fever encephalitis, with particular emphasis on epidemiology, virology, neurobiology, neuropathology, clinical manifestations, diagnosis, treatment, prognosis, and future research directions. By integrating findings from clinical investigations, survivor studies, experimental models, and contemporary outbreak experiences, this review aims to provide a comprehensive overview of the neurological dimensions of Ebola virus disease and to highlight areas requiring further scientific investigation.

METHODS

This descriptive review was conducted to synthesize contemporary evidence regarding the neurological manifestations, neuropathogenesis, diagnosis, management, and long-term outcomes of Ebola hemorrhagic fever encephalitis. The review was designed as a narrative and descriptive synthesis rather than a systematic review or meta-analysis because of the heterogeneity of available evidence and the relative scarcity of large-scale controlled neurological studies.

A comprehensive literature search was performed using PubMed/MEDLINE, Web of Science, and Google Scholar databases. The search period encompassed studies published between January 2010 and June 2026 to capture evidence generated during and after the major West African Ebola epidemic, as well as subsequent outbreaks in the Democratic Republic of Congo and other affected regions. Additional landmark studies published before 2010 were included when considered historically or scientifically essential to understanding Ebola virology, pathogenesis, or neurological disease. Search terms included combinations of "Ebola virus disease," "Ebola hemorrhagic fever," "Ebola encephalitis," "meningoencephalitis," "neurological complications," "central nervous system," "neuroinflammation," "neuropathology," "viral persistence," "blood-brain barrier," "survivor syndrome," "cognitive dysfunction," "seizures," "neuroimmunology," and "post-Ebola syndrome." Reference lists of selected articles were manually reviewed to identify additional relevant studies.

Eligible publications included original research articles, observational studies, cohort studies, case-control investigations, clinical trials, neuropathological studies, neuroimaging studies, case reports, case series, public health reports, outbreak investigations, and authoritative review articles that provided information relevant to neurological aspects of Ebola virus disease. Studies addressing virology, immunology, pathogenesis, clinical manifestations, diagnosis, treatment, rehabilitation, survivor outcomes, or public health implications were considered for inclusion.

Exclusion criteria included non-English publications lacking accessible translations, conference abstracts without sufficient methodological detail, duplicate publications, purely veterinary studies without translational relevance to human disease, and articles focusing exclusively on non-neurological aspects of Ebola virus disease without relevance to central or peripheral nervous system involvement.

Data were synthesized qualitatively. Given the heterogeneity of study designs, patient populations, outcome measures, and diagnostic methodologies, formal meta-analysis was not performed. Instead, findings were organized thematically according to epidemiology, virology, neurobiology, neuropathology, clinical presentation, diagnosis, treatment, prognosis, and future directions. Particular emphasis was placed on studies providing direct evidence of CNS involvement, neurological complications, viral persistence, and long-term survivor outcomes.

Epidemiology

Ebola virus disease (EVD) remains one of the most devastating zoonotic infectious diseases affecting human populations. Since its initial recognition in 1976, recurrent outbreaks have occurred predominantly throughout Central and West Africa, producing substantial mortality, socioeconomic disruption, and long-term health consequences among survivors.[1–4] Although Ebola virus disease has historically been characterized primarily as an acute viral hemorrhagic fever, increasing evidence indicates that neurological complications constitute an important but previously underrecognized component of the disease burden.[7–12]

The first recognized outbreaks occurred simultaneously in Yambuku, Zaire (now the Democratic Republic of Congo) and Nzara, Sudan, in 1976. These outbreaks resulted in case fatality rates approaching 88% and 53%, respectively, and established Ebola virus disease as one of the most lethal infectious diseases known to affect humans (1,60). During these early epidemics, neurological manifestations received limited attention because of overwhelming mortality, limited diagnostic infrastructure, and the urgent need to control transmission. Nevertheless, retrospective analyses

suggest that headache, confusion, delirium, and altered consciousness were frequently observed among affected individuals.[2,60]

Subsequent outbreaks throughout the Democratic Republic of Congo, Uganda, Gabon, the Republic of Congo, and South Sudan further expanded understanding of the disease. Investigations conducted during the Kikwit outbreak of 1995 documented altered mental status, encephalopathy, and progressive neurological deterioration among severely affected patients.[60] Similarly, outbreaks in Uganda between 2000 and 2001 reported frequent headache, confusion, and reduced consciousness, suggesting that CNS involvement was more common than previously appreciated.[59]

The epidemiological landscape of Ebola virus disease changed dramatically during the West African epidemic of 2014–2016. This unprecedented outbreak affected Guinea, Liberia, and Sierra Leone and resulted in more than 28,000 reported cases and over 11,000 deaths, making it the largest Ebola epidemic in recorded history.[4] Beyond its immediate mortality impact, the epidemic generated an unprecedented population of survivors, thereby creating opportunities to investigate long-term clinical outcomes and chronic sequelae.

The availability of large survivor cohorts fundamentally transformed understanding of Ebola-associated neurological disease. Multiple studies conducted among survivors demonstrated persistent neurological symptoms occurring at substantially higher frequencies than among uninfected controls.[10–12,14–20] Headaches emerged as one of the most common complaints, affecting a substantial proportion of survivors months and even years after recovery. Cognitive dysfunction, memory impairment, sleep disturbances, depression, anxiety, tremor, neuropathic pain, and visual abnormalities were also reported with remarkable frequency.[10–12,18–20]

The PREVAIL III study conducted in Liberia provided some of the most comprehensive epidemiological data regarding post-Ebola neurological sequelae.[14] Longitudinal follow-up demonstrated that survivors experienced significantly higher rates of neurological symptoms compared with close contacts who had not been infected. Importantly, many manifestations persisted despite apparent virological recovery, suggesting that neurological injury may represent a chronic consequence of infection rather than a transient post-illness phenomenon.

Several investigations have attempted to quantify the burden of neurological complications among survivors. Although estimates vary according to study design and outcome definitions, available evidence suggests that between one-quarter and two-thirds of survivors experience at least one persistent neurological symptom during follow-up.[18–20,31] Headache remains the most frequently reported manifestation, followed by cognitive impairment, memory difficulties, sleep disturbances, neuropathic pain, depression, and anxiety disorders.[18–20,31]

The epidemiology of acute neurological complications is more difficult to define because many outbreaks occurred in settings lacking advanced neurological assessment. Nevertheless, available data indicate that encephalopathy, delirium, seizures, focal neurological deficits, and meningoencephalitis occur with sufficient frequency to warrant routine neurological evaluation during acute infection.[7–10,24] Severe neurological manifestations appear to be associated with higher viral loads, more intense systemic inflammatory responses, and increased mortality risk.[5,6,43]

One of the most significant epidemiological developments in recent years has been recognition of persistent viral reservoirs within immune-privileged anatomical compartments. Detection of Ebola viral RNA within cerebrospinal fluid, ocular fluid, semen, and other tissues months after apparent recovery has challenged traditional assumptions

regarding viral clearance.[22,23,24] The demonstration of delayed meningoencephalitis associated with persistent CNS infection has further highlighted the long-term neurological risks faced by survivors.[8,9,12]

Age appears to influence neurological outcomes. Pediatric survivors may experience developmental delay, cognitive impairment, behavioral abnormalities, educational difficulties, and psychosocial dysfunction that persist long after recovery.[29,69] Because childhood represents a critical period for neurodevelopment, CNS injury sustained during Ebola infection may have lifelong consequences for affected individuals. Unfortunately, epidemiological data regarding pediatric neurological outcomes remain relatively limited compared with adult survivor cohorts.

Sex-specific differences have also been investigated. Although mortality rates appear broadly similar between men and women after adjustment for disease severity, several studies suggest differences in patterns of long-term sequelae and viral persistence.[22,31] Persistent viral RNA within the male reproductive tract has received particular attention because of its implications for transmission dynamics and immune-privileged reservoirs.[22] Whether such differences directly influence neurological outcomes remains incompletely understood.

Recent outbreaks in the Democratic Republic of Congo have further expanded understanding of Ebola-associated neurological disease. Improved surveillance systems, enhanced diagnostic capabilities, and increased awareness among clinicians have facilitated identification of neurological complications that may previously have gone unrecognized.[12,21] Reports of delayed meningoencephalitis, persistent neurocognitive dysfunction, movement disorders, and chronic psychiatric symptoms continue to reinforce the importance of long-term neurological monitoring among survivors.

From a public health perspective, the epidemiology of Ebola encephalitis extends beyond traditional measures of incidence and mortality. Neurological complications contribute substantially to disability-adjusted life years, healthcare utilization, reduced workforce participation, educational disruption, and diminished quality of life.[18–20,31] Consequently, the burden of neurological disease may persist for years after transmission has ceased, creating ongoing challenges for healthcare systems and affected communities.

Climate change, environmental degradation, deforestation, population growth, urbanization, and increased human-wildlife interactions may further influence future Ebola epidemiology.[30,31] These ecological changes may increase opportunities for zoonotic spillover events and thereby expand the population at risk for both acute Ebola infection and its neurological sequelae. As a result, understanding the epidemiology of Ebola encephalitis will become increasingly important for outbreak preparedness and global health planning.

Collectively, available evidence demonstrates that neurological involvement is neither rare nor incidental in Ebola virus disease. Rather, neurological manifestations represent an integral component of the disease spectrum, contributing significantly to both acute morbidity and long-term disability. Continued epidemiological surveillance, standardized neurological assessments, and prospective survivor studies will be essential for defining the true burden of Ebola-associated CNS disease and informing future clinical and public health interventions.

Structural and Genomic Classification and Morphology

Ebola viruses belong to the family *Filoviridae*, a group of filamentous enveloped RNA viruses within the order *Mononegavirales*. Recent taxonomic revisions by the International Committee on Taxonomy of Viruses have refined

classification within this family while preserving the clinical relevance of traditionally recognized Ebola virus species.[1] Members of the genus responsible for human disease include *Zaire ebolavirus*, *Sudan ebolavirus*, *Bundibugyo ebolavirus*, *Taï Forest ebolavirus*, *Reston ebolavirus*, and the more recently identified *Bombali ebolavirus*.[1,30]

Among these species, *Zaire ebolavirus* is responsible for the majority of large outbreaks and exhibits the highest case-fatality rates. The 2014–2016 West African epidemic and multiple subsequent outbreaks in the Democratic Republic of Congo were caused by this species and have provided much of the contemporary knowledge regarding Ebola-associated neurological disease.[3,4,21] In contrast, *Sudan ebolavirus* has been responsible for recurrent outbreaks in Uganda and Sudan, whereas *Bundibugyo ebolavirus* has generally been associated with somewhat lower mortality rates.[29,59]

Morphologically, Ebola virions possess a distinctive filamentous appearance that differentiates them from many other medically important viruses. Electron microscopy demonstrates elongated pleomorphic particles that may appear as filaments, loops, circles, or shepherd's crook configurations.[35] Virions typically measure approximately 80 nm in diameter and may range from several hundred nanometers to more than 10 μm in length, although particles between 800 and 1,200 nm are most commonly observed.[35,39]

The virion consists of a host-derived lipid envelope containing trimeric glycoprotein spikes that project outward from the viral surface. These glycoproteins play essential roles in host-cell attachment, receptor binding, membrane fusion, and cellular entry.[35,36] Beneath the envelope lies a matrix layer composed primarily of VP40 and VP24 proteins that contribute to structural integrity and viral assembly.[27,33]

The viral genome is a non-segmented, negative-sense, single-stranded RNA molecule approximately 19 kilobases in length.[32,33] The genome encodes seven major structural proteins arranged in the order NP–VP35–VP40–GP–VP30–VP24–L. Each protein contributes to specific aspects of viral replication, immune evasion, assembly, or pathogenesis.

The glycoprotein encoded by the GP gene represents one of the most important determinants of virulence and neuroinvasion. In addition to facilitating cellular entry, GP contributes to endothelial dysfunction, vascular permeability, and blood-brain barrier disruption, processes that are increasingly recognized as central to Ebola-associated neurological injury.[23–26,36] Experimental evidence suggests that GP-mediated endothelial damage may facilitate CNS entry by permitting passage of viral particles and inflammatory mediators into neural tissues. The structure is shown below.[91]

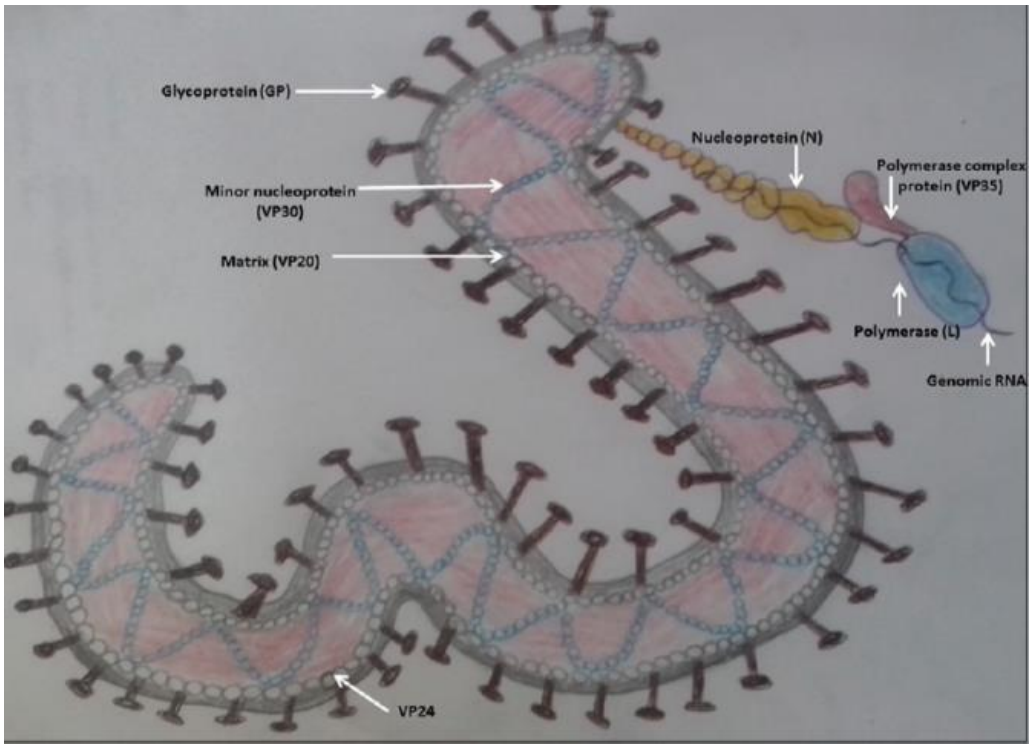

Figure 1: The Ebola virion [*Source: El Sayed et al; 2016*]

Neurobiology, Neuroimmunology, and Neuropathology of Ebola Hemorrhagic Fever Encephalitis

The recognition of Ebola virus disease as a neuroinvasive and neuroinflammatory disorder represents one of the most significant developments in contemporary filovirus research. Although Ebola virus disease was historically regarded as a systemic viral hemorrhhagic fever characterized primarily by vascular injury, coagulopathy, immune dysregulation, and multiorgan failure, accumulating evidence now demonstrates substantial involvement of both the central and peripheral nervous systems.[7–12] Neurological complications may occur during acute infection, convalescence, or many months after apparent recovery, indicating that neural tissues constitute important targets of Ebola virus-associated injury.

The neurobiology of Ebola encephalitis is complex and multifactorial. Current evidence suggests that neurological injury arises through the combined effects of direct viral neuroinvasion, cytokine-mediated neuroinflammation, endothelial dysfunction, blood-brain barrier disruption, cerebrovascular injury, immune-mediated tissue damage, and persistent viral reservoirs within immune-privileged anatomical compartments.[8,9,13,24,26] These interacting mechanisms contribute to the diverse spectrum of acute and chronic neurological manifestations observed among patients and survivors.

Ebola Virus Transmission

Ebola virus disease is a zoonotic infection that originates from complex ecological interactions between wildlife reservoirs, susceptible animal hosts, and humans. Current evidence strongly supports fruit bats, particularly members of the family *Pteropodidae*, as the principal natural reservoir of ebolaviruses. Serological, molecular, and ecological investigations have demonstrated evidence of Ebola virus infection in several fruit bat species without apparent disease, suggesting their role in maintaining viral circulation within endemic ecosystems.[30,31] The discovery of Bombali virus

in bats further strengthened the hypothesis that chiropteran species serve as important hosts for ebolaviruses and contribute to long-term viral maintenance in nature.[30]

Transmission from wildlife to humans occurs through zoonotic spillover events involving direct contact with infected animals, animal carcasses, blood, secretions, tissues, or contaminated environmental materials. Non-human primates, including chimpanzees and gorillas, as well as forest antelopes and other mammals, may become infected following exposure to infected bat populations and subsequently serve as intermediate hosts for human infection.[2,3,31] Numerous outbreaks have been linked to hunting, butchering, preparation, and consumption of bushmeat, activities that facilitate direct exposure to infectious body fluids and tissues.[2–4,49]

Following zoonotic introduction, Ebola virus spreads efficiently through human-to-human transmission. The virus is transmitted primarily through direct contact of broken skin or mucous membranes with infected blood, vomitus, feces, urine, saliva, breast milk, semen, vaginal secretions, sweat, tears, and other bodily fluids from symptomatic individuals.[3,24,49,50,90] Viral transmission is particularly efficient during advanced stages of illness because viral loads increase substantially as disease progresses, resulting in greater concentrations of infectious particles within bodily fluids.[5,6,43,65]

Healthcare-associated transmission has played a major role in the amplification of several Ebola outbreaks. Exposure of healthcare workers to infected blood and secretions, inadequate use of personal protective equipment, reuse of contaminated medical equipment, and delayed recognition of cases have contributed significantly to nosocomial transmission events.[4,24,49,50,86] During the West African epidemic, healthcare settings represented important focal points for secondary transmission, highlighting the critical importance of infection prevention and control practices.[4,86–89]

Traditional funeral and burial practices have also been recognized as important drivers of Ebola transmission. Individuals who prepare bodies for burial may come into contact with highly infectious blood and secretions because viral replication continues after death and viral concentrations often remain extremely high within cadaveric tissues. Epidemiological investigations from multiple outbreaks demonstrated that funeral-associated exposures contributed substantially to community transmission and outbreak propagation.[4,49,58–60]

Unlike respiratory viruses such as influenza and SARS-CoV-2, Ebola virus is not generally transmitted through airborne spread under natural conditions. Transmission typically requires direct contact with infectious body fluids or contaminated fomites. Consequently, rapid case identification, patient isolation, contact tracing, environmental decontamination, safe burial practices, and strict adherence to infection-control measures remain highly effective strategies for interrupting transmission chains.[24,49,50,86–89]

An important additional transmission pathway involves viral persistence among survivors. Ebola virus may persist within immune-privileged sites including the testes, ocular tissues, central nervous system, and mammary glands long after apparent recovery from acute illness.[8,12,13,22,23] Persistent viral RNA has been detected in semen for months or even years following recovery, and documented cases of sexual transmission from survivors have confirmed the epidemiological significance of this phenomenon.[22] Similarly, persistence of Ebola virus within ocular fluids and cerebrospinal fluid has been associated with delayed clinical relapse and recurrent disease manifestations.[8,12,13,23]

The transmission cycle of Ebola virus therefore consists of several interconnected stages. The virus is maintained within wildlife reservoirs, particularly fruit bats, from which zoonotic spillover may occur to susceptible mammals and humans. Once introduced into human populations, transmission occurs primarily through direct exposure to infectious bodily fluids, healthcare-associated contact, funeral practices, and, less commonly, persistent viral reservoirs among survivors. Understanding these transmission pathways remains fundamental for outbreak prevention, public health preparedness, surveillance programs, and effective clinical management of Ebola virus disease.[2–4,24,49,50,90] The viral transmission is shown below;

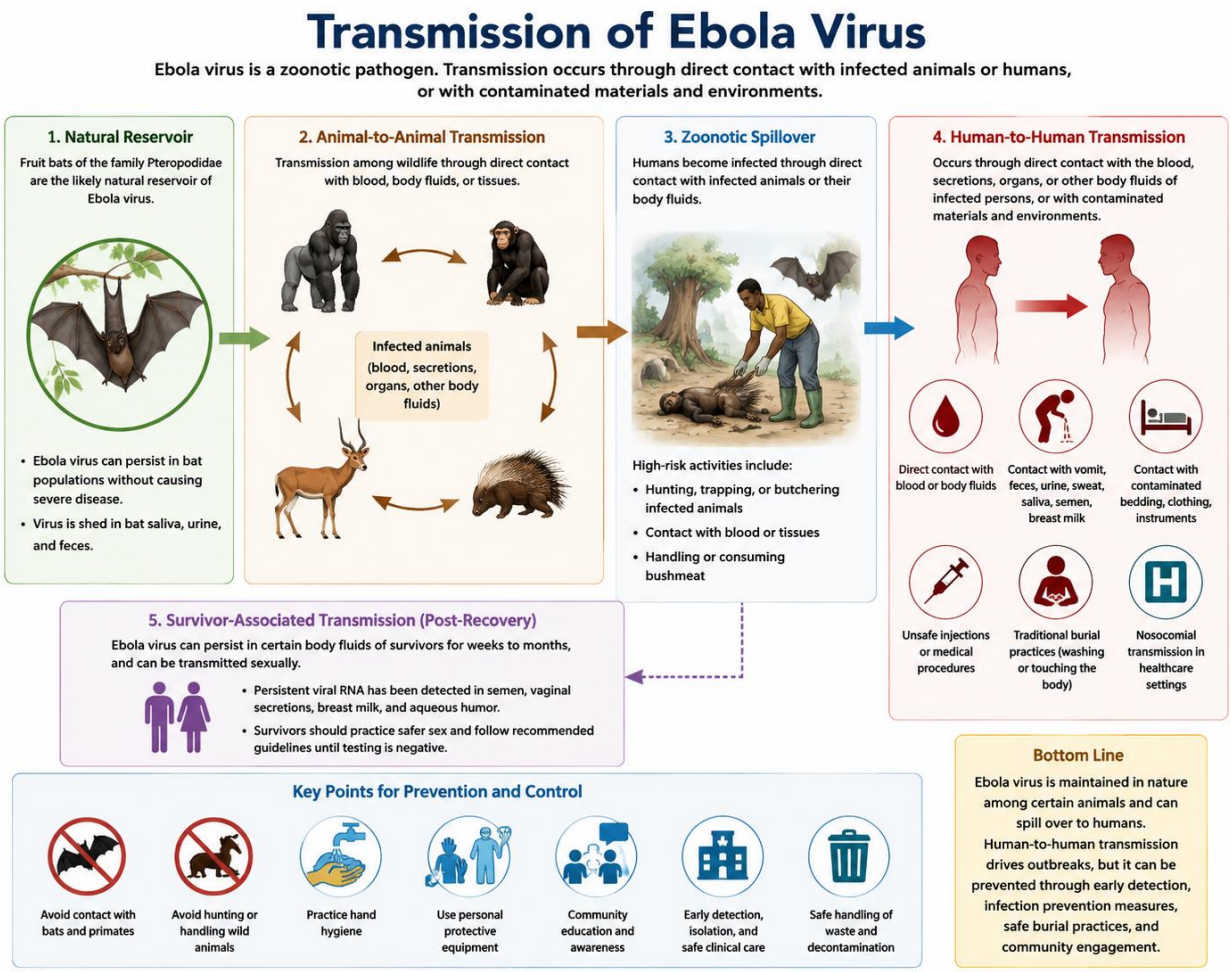

Figure 2: Ebola Viral Transmission.

Mechanisms of Central Nervous System Invasion

One of the fundamental questions in Ebola neuropathogenesis concerns how the virus gains access to the central nervous system. Under normal physiological conditions, the blood-brain barrier serves as a highly specialized protective interface that restricts entry of pathogens, inflammatory mediators, and circulating immune cells into neural tissues. Nevertheless, multiple lines of evidence indicate that Ebola virus can overcome these protective barriers and establish infection within the CNS.[24–26]

The most widely accepted mechanism involves hematogenous dissemination during systemic viremia. Following infection, Ebola virus replicates extensively within monocytes, macrophages, and dendritic cells, generating extraordinarily high circulating viral loads in severe disease.[26,39] These infected immune cells disseminate throughout

the body and may function as Trojan horse vehicles that transport viral particles across vascular barriers. Migration of infected leukocytes into neural tissues may therefore provide one pathway through which Ebola virus gains access to the CNS.[19,27]

A second major mechanism involves disruption of blood-brain barrier integrity. Severe Ebola virus disease is characterized by profound cytokine activation and endothelial injury. Elevated concentrations of tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, interferon-gamma, monocyte chemoattractant protein-1, macrophage inflammatory proteins, and numerous additional inflammatory mediators induce endothelial dysfunction and compromise tight-junction integrity.[23–26,40,41] The resulting increase in vascular permeability facilitates entry of viral particles, infected leukocytes, and inflammatory mediators into neural tissues.

Experimental studies have further suggested that the choroid plexus and ventricular system may serve as portals of CNS entry. Animal investigations have demonstrated persistent viral infection within ventricular structures despite apparent clearance from peripheral organs, supporting the hypothesis that cerebrospinal fluid pathways may represent important sites of neuroinvasion and long-term viral persistence.[12,24]

The glycoprotein of Ebola virus also appears to contribute directly to neuroinvasion. Beyond its essential role in cellular entry, viral glycoprotein induces endothelial activation, vascular permeability, and cellular injury. These effects may further compromise blood-brain barrier integrity and promote CNS dissemination.[35,36] This is described below;

Table 1: Ebola Viral Proteins and Neuropathogenic Relevance.

Protein	Function	Neurological Relevance
NP	Nucleocapsid formation	Supports viral replication
VP35	Polymerase cofactor	Suppresses interferon signaling
VP40	Matrix protein	Viral assembly and budding
GP	Host-cell attachment and entry	Endothelial injury and BBB disruption
VP30	Transcription activation	Enhances viral gene expression
VP24	Immune evasion	Inhibits STAT1 signaling
L	RNA polymerase	Viral replication

Neuroimmunology of Ebola Virus Infection

Neuroimmune activation represents a central component of Ebola encephalitis. Unlike certain viral encephalitides in which direct neuronal infection predominates, neurological injury in Ebola virus disease frequently reflects a combination of viral replication and dysregulated host immune responses.[17,26,27]

One of the defining features of severe Ebola virus disease is the development of a cytokine storm. Infected monocytes, macrophages, dendritic cells, endothelial cells, and other host cells release large quantities of proinflammatory cytokines and chemokines that contribute to systemic disease severity.[40,41] While these responses initially function as antiviral defense mechanisms, excessive cytokine production ultimately becomes pathological.

Within the CNS, elevated concentrations of inflammatory mediators promote recruitment of leukocytes, activation of resident immune cells, disruption of neuronal homeostasis, and amplification of local inflammatory responses. The resulting neuroinflammatory environment contributes to neuronal dysfunction, synaptic injury, cerebral edema, and altered neurotransmission.[17,26]

Several studies have demonstrated that fatal Ebola virus infection is associated with profound immune dysregulation characterized by defective adaptive immune responses, widespread lymphocyte apoptosis, and uncontrolled innate immune activation.[40,41] This imbalance may contribute to both inadequate viral clearance and excessive tissue injury, thereby exacerbating neurological damage.

The contribution of immune-mediated mechanisms is supported by observations that neurological symptoms may persist despite apparent clearance of systemic infection. Such findings suggest that chronic neuroinflammation may continue even after active viral replication has diminished, thereby contributing to long-term neurological sequelae among survivors.[17,18,31]

Microglial Activation

Microglia are the principal resident immune cells of the central nervous system and play critical roles in host defense, synaptic regulation, and maintenance of neural homeostasis. During Ebola virus infection, microglia become activated in response to viral antigens, inflammatory cytokines, and tissue injury.

Activated microglia undergo morphological and functional changes characterized by proliferation, migration, cytokine production, reactive oxygen species generation, and enhanced phagocytic activity. While these responses may initially contribute to pathogen clearance, excessive or prolonged activation can produce substantial collateral neuronal damage.[17,27]

Persistent microglial activation has been implicated in numerous neurodegenerative and neuroinflammatory disorders and may similarly contribute to chronic neurological symptoms observed among Ebola survivors. Ongoing release of inflammatory mediators may impair neuronal function, alter synaptic plasticity, and contribute to cognitive dysfunction, depression, fatigue, and chronic pain syndromes.[18–20,31]

Astrocyte Dysfunction and Reactive Gliosis

Astrocytes constitute the most abundant glial cell population within the CNS and perform essential functions related to blood-brain barrier maintenance, neurotransmitter regulation, metabolic support, ion homeostasis, and neuronal survival. During Ebola-associated neuroinflammation, astrocytes become activated and undergo reactive gliosis.

Reactive astrocytes exhibit hypertrophy, increased expression of glial fibrillary acidic protein, altered metabolic activity, and enhanced production of cytokines and chemokines. Although these responses may initially protect neural tissues, prolonged astrocyte activation can contribute to chronic inflammation and neuronal dysfunction.

Astrocytic impairment may also interfere with glutamate regulation, thereby promoting excitotoxic injury. Excess extracellular glutamate can result in neuronal hyperexcitability, calcium influx, oxidative stress, and eventual neuronal death. Such mechanisms may contribute to seizures, encephalopathy, and long-term cognitive dysfunction observed among affected patients.[17,27,34]

Endothelial Dysfunction and Blood-Brain Barrier Injury

Endothelial injury represents a hallmark of Ebola virus disease and occupies a central position in current models of neuropathogenesis. The cerebral microvascular endothelium forms a critical component of the blood-brain barrier, regulating molecular exchange between the circulation and neural tissues.

During severe infection, viral glycoprotein, inflammatory cytokines, coagulation abnormalities, and oxidative stress collectively disrupt endothelial integrity. Tight junctions become compromised, vascular permeability increases, and inflammatory cells gain access to neural tissues.[23–26,36]

The resulting blood-brain barrier dysfunction permits entry of circulating cytokines, immune complexes, viral particles, and infected leukocytes into the CNS. This process amplifies neuroinflammation and contributes to cerebral edema, neuronal injury, and neurological dysfunction.

Endothelial injury may also impair cerebral autoregulation and microvascular perfusion. Reduced cerebral blood flow, combined with systemic hypotension and coagulopathy, may produce secondary ischemic injury that further contributes to neurological deterioration. This is shown below;

Table 2: Major Mechanisms of Neurological Injury in Ebola Virus Disease.

Mechanism	Pathological Effect
Direct neuroinvasion	Viral infection of CNS structures
Cytokine storm	Neuroinflammation and neuronal dysfunction
Blood-brain barrier disruption	Increased CNS permeability
Endothelial injury	Cerebral edema and hemorrhage
Microvascular thrombosis	Cerebral ischemia
Persistent CNS reservoirs	Delayed neurological relapse
Microglial activation	Chronic neuroinflammation
Astrocyte dysfunction	Impaired neural homeostasis

Cerebrovascular Pathology

Vascular pathology is increasingly recognized as an important contributor to neurological injury during Ebola virus disease. Coagulation abnormalities, endothelial dysfunction, inflammatory activation, and microvascular thrombosis interact to produce complex cerebrovascular disturbances.[26,39]

Microvascular thrombosis may impair oxygen delivery and nutrient transport to neural tissues, resulting in ischemic injury and neuronal loss. Simultaneously, endothelial disruption increases susceptibility to vascular leakage and hemorrhage. These mechanisms may explain reports of stroke-like syndromes, focal neurological deficits, and intracranial hemorrhagic lesions among affected individuals.[17,24]

Cerebral hypoperfusion may be further exacerbated by shock, dehydration, and systemic circulatory failure. Consequently, neurological injury frequently reflects a combination of direct viral effects and secondary vascular compromise.

Neuropathological Findings

Direct neuropathological investigations remain relatively limited because of biosafety concerns and logistical challenges associated with autopsy studies. Nevertheless, available human and experimental data provide important insights into the structural consequences of CNS infection.

Gross pathological findings include cerebral edema, meningeal congestion, vascular engorgement, and multifocal hemorrhagic lesions. In severe cases, diffuse brain swelling may contribute to elevated intracranial pressure and neurological deterioration.[27,39]

Microscopically, investigators have reported perivascular inflammatory infiltrates composed predominantly of macrophages and lymphocytes, reactive astrogliosis, diffuse microglial activation, neuronal degeneration, focal necrosis, white matter injury, microvascular thrombosis, and meningeal inflammation.[17,27,39]

Perivascular inflammation appears particularly prominent and supports the concept that vascular and immune-mediated mechanisms play major roles in disease pathogenesis. Similarly, the widespread activation of glial cells suggests that chronic neuroinflammation may contribute to persistent neurological symptoms long after acute infection has resolved. The suggested neuropathogenesis is shown below;

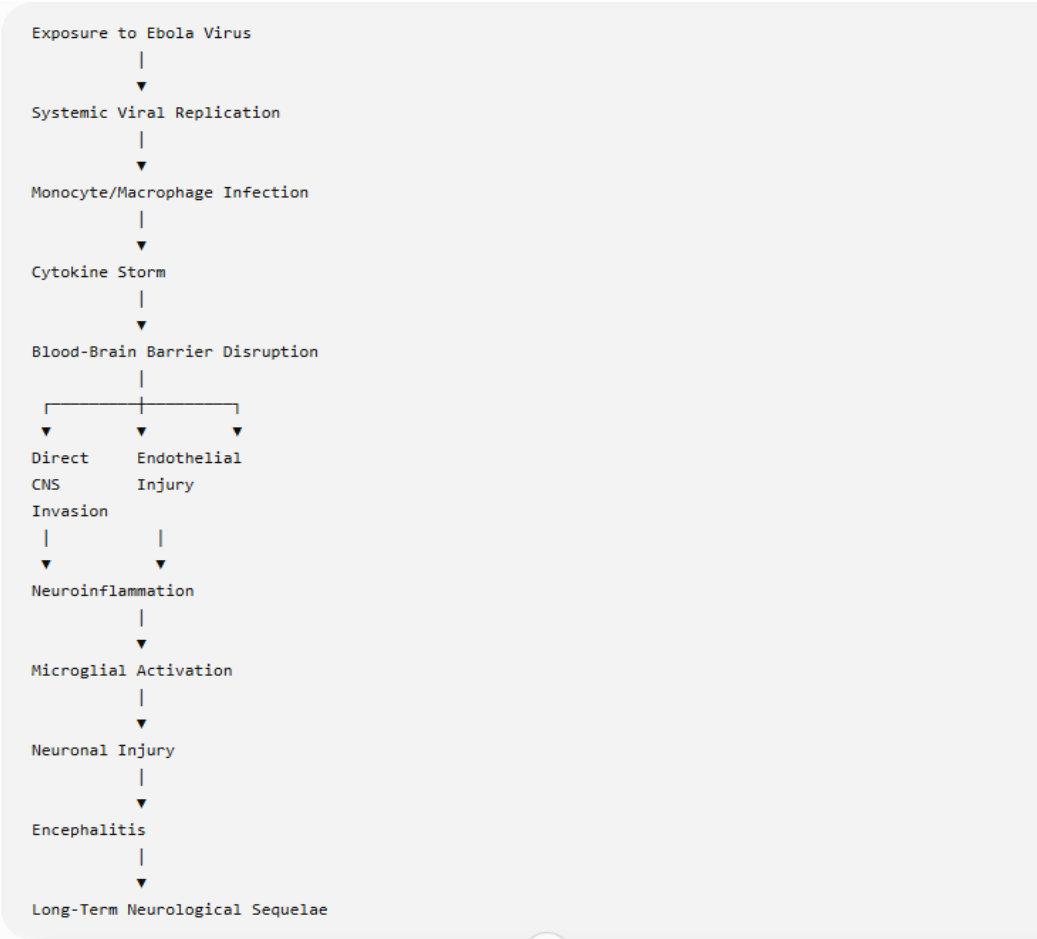

Figure 3: Suggested Neuropathogenesis of Ebola Encephalitis.

The distribution of neuropathological abnormalities varies among patients and likely reflects differences in viral burden, immune responses, treatment timing, and host susceptibility. Further neuropathological investigations will be necessary to fully characterize the anatomical and cellular targets of Ebola virus within the nervous system. The neuropathological findings are shown below;

Table 3: Neuropathological Findings in Ebola Hemorrhagic Fever Encephalitis.

Pathology	Description
Cerebral edema	Diffuse swelling of brain tissue
Meningeal inflammation	Lymphocytic infiltration
Reactive gliosis	Astrocyte proliferation
Microglial activation	Neuroimmune activation

Neuronal degeneration	Direct and indirect injury
Perivascular inflammation	Macrophage-rich infiltrates
Microvascular thrombosis	Ischemic injury
Multifocal hemorrhage	Vascular disruption
White matter injury	Demyelination and axonal injury

Viral Persistence Within the Central Nervous System

Perhaps the most transformative discovery in recent Ebola neuroscience has been the demonstration of persistent viral reservoirs within immune-privileged compartments. Several landmark investigations have documented Ebola viral RNA within cerebrospinal fluid months after apparent recovery and clearance of virus from peripheral blood.[8,9,12,13,24]

The case reported by Jacobs and colleagues remains particularly influential. Approximately nine months after recovery from acute Ebola virus disease, a healthcare worker developed severe meningoencephalitis accompanied by detection of Ebola viral RNA within cerebrospinal fluid despite negative blood testing.[8] This observation provided compelling evidence that the CNS may function as a reservoir capable of sustaining prolonged viral persistence.

Subsequent reports from the Democratic Republic of Congo have further documented fatal meningoencephalitis associated with persistent Ebola infection within neural tissues.[12] These findings fundamentally altered prevailing assumptions regarding viral clearance and recovery.

Persistent CNS infection may contribute to delayed neurological relapse, chronic neuroinflammation, and long-term neurological dysfunction. The mechanisms permitting viral persistence remain incompletely understood but likely involve limited immune surveillance within immune-privileged compartments, viral immune-evasion strategies, and complex host-pathogen interactions.

The recognition of viral persistence has profound implications for survivor care, surveillance programs, therapeutic development, and future outbreak preparedness. Continued investigation of CNS reservoirs will be essential for understanding the full neurological burden of Ebola virus disease.

Long-Term Neurocognitive Consequences

One of the most significant developments emerging from post-Ebola survivor research has been the recognition of persistent neurocognitive dysfunction. Although early outbreak investigations focused primarily on mortality and acute systemic complications, longitudinal follow-up studies have demonstrated that cognitive impairment remains a common and clinically important consequence of Ebola virus disease.[10–12,14,18–20,31]

Neurocognitive abnormalities affect multiple domains, including attention, working memory, executive function, information processing speed, verbal fluency, and visuospatial performance. Survivors frequently report difficulties concentrating, impaired short-term memory, reduced mental stamina, and diminished occupational or academic performance. Such symptoms may persist for years after apparent clinical recovery and often occur even in individuals without documented acute encephalitis.[18–20,31]

The biological basis of these cognitive deficits remains incompletely understood. Current evidence suggests that chronic neuroinflammation plays a central role. Persistent activation of microglia and astrocytes may alter neuronal signaling, impair synaptic plasticity, and disrupt functional neural networks involved in learning and memory.

Additionally, endothelial dysfunction, microvascular injury, and blood-brain barrier abnormalities may contribute to chronic cerebral hypoperfusion and progressive neuronal dysfunction.[17,24,26,34]

Neuroimaging studies performed in survivors remain relatively limited; however, available investigations suggest that structural and functional abnormalities may persist beyond the acute phase of infection. White matter injury, inflammatory changes, microvascular pathology, and alterations in functional connectivity have all been proposed as contributors to long-term neurocognitive impairment.[31,34]

Importantly, cognitive dysfunction exerts substantial socioeconomic consequences. Survivors experiencing persistent neurocognitive deficits frequently encounter difficulties returning to work, resuming educational activities, or participating fully in community life. These impairments therefore represent not only medical complications but also significant public health and developmental challenges in affected regions.

Neuropsychiatric Manifestations

Neuropsychiatric complications are increasingly recognized as integral components of the neurological spectrum of Ebola virus disease. Depression, anxiety disorders, post-traumatic stress disorder, sleep disturbances, emotional dysregulation, and chronic fatigue occur at significantly higher frequencies among survivors than among uninfected populations.[18–20,31]

The origins of these manifestations are multifactorial. Direct neurological injury may alter neural circuits involved in mood regulation and emotional processing. Persistent neuroinflammation may influence neurotransmitter systems, hypothalamic-pituitary-adrenal axis activity, and neuroendocrine regulation. Simultaneously, survivors often experience substantial psychosocial stressors, including bereavement, social stigma, economic hardship, and prolonged healthcare utilization.[18–20]

Depressive symptoms represent one of the most frequently reported psychiatric sequelae. Multiple cohort studies have documented elevated rates of major depressive symptoms among survivors, often accompanied by reduced quality of life, impaired social functioning, and diminished occupational productivity.[18,20,31] Anxiety disorders similarly contribute to long-term disability and may coexist with depression, sleep disturbances, and chronic pain syndromes.

Post-traumatic stress disorder has also emerged as a significant concern. Many survivors witnessed the deaths of family members, experienced prolonged isolation during treatment, or endured severe life-threatening illness. Such experiences may result in persistent intrusive memories, hypervigilance, emotional distress, and avoidance behaviors that interfere with recovery and reintegration.[20,31]

Sleep disturbances further complicate the clinical picture. Insomnia, fragmented sleep, nightmares, excessive daytime fatigue, and altered circadian rhythms have been reported in survivor cohorts. Sleep disruption may exacerbate cognitive dysfunction, psychiatric symptoms, pain syndromes, and overall quality of life, thereby creating a self-perpetuating cycle of neurological morbidity.

Peripheral Nervous System Involvement

Although central nervous system complications have received greater scientific attention, increasing evidence suggests that Ebola virus disease also affects the peripheral nervous system. Survivors frequently report sensory disturbances, neuropathic pain, paresthesias, muscle weakness, autonomic dysfunction, and reduced exercise tolerance.[18–20,31]

Neuropathic pain is among the most commonly reported peripheral neurological manifestations. Patients often describe burning sensations, tingling, numbness, electric-shock-like discomfort, or diffuse pain involving the extremities. These symptoms may persist for months or years following recovery and can substantially impair daily functioning.[18,20]

The mechanisms responsible for peripheral nervous system injury remain incompletely understood. Potential contributors include direct viral effects, immune-mediated neuropathy, inflammatory injury, vascular dysfunction, nutritional deficiencies, and critical illness-associated neuropathy. Persistent inflammatory activation may play a particularly important role in sustaining chronic neuropathic symptoms long after acute infection has resolved.

Motor dysfunction has also been reported among survivors. Muscle weakness, impaired coordination, gait abnormalities, and reduced endurance may reflect combined contributions from peripheral nerve injury, central nervous system pathology, musculoskeletal complications, and prolonged hospitalization. Rehabilitation programs therefore represent essential components of survivor care.

Autonomic nervous system involvement remains poorly studied but may contribute to orthostatic intolerance, cardiovascular dysregulation, gastrointestinal symptoms, and thermoregulatory abnormalities reported by some survivors. Further investigation of autonomic dysfunction may reveal additional dimensions of Ebola-associated neurological disease that have thus far received limited attention.

Cranial Neuropathies and Sensory Dysfunction

Cranial nerve involvement represents another important neurological consequence of Ebola virus disease. Visual disturbances are particularly common and may arise from direct ocular infection, optic nerve involvement, retinal pathology, or inflammatory ocular disease. The demonstration of persistent Ebola virus within ocular fluids has highlighted the eye as an immune-privileged reservoir and underscored the interconnected nature of neurological and ophthalmological complications.[23]

Affected individuals may experience blurred vision, reduced visual acuity, photophobia, floaters, visual field defects, or complete vision loss. Uveitis has emerged as one of the most significant ophthalmological complications among survivors and may contribute to long-term visual disability if left untreated.[23]

Hearing impairment has also been reported among survivors, although it appears less common than visual abnormalities. Tinnitus, reduced auditory acuity, and vestibular dysfunction may occur in association with cranial nerve involvement or broader neurological injury. Such manifestations may further complicate social reintegration and quality of life.

Additional cranial neuropathies involving facial movement, swallowing, speech production, and ocular motility have been described. Although relatively uncommon, these findings provide further evidence that Ebola virus disease may affect multiple levels of the nervous system.

Pediatric Neurobiology and Neurological Outcomes

Children represent a particularly vulnerable population in the context of Ebola virus disease. The developing nervous system may exhibit unique susceptibility to inflammatory injury, metabolic disturbances, and viral infection. Consequently, neurological complications occurring during childhood may have lifelong consequences extending well beyond the acute illness.[29,69]

Pediatric survivors have been reported to experience cognitive impairment, developmental delay, learning difficulties, behavioral abnormalities, emotional dysregulation, and social challenges following recovery. Because many affected children reside in regions with limited access to developmental assessment and specialized educational services, the true burden of pediatric neurological disability may be substantially underestimated.

The mechanisms underlying pediatric neurological injury likely overlap with those observed in adults but may be amplified by the vulnerability of developing neural circuits. Neuroinflammation occurring during critical periods of brain maturation may alter synaptic development, myelination, and neuronal connectivity, thereby influencing long-term cognitive and behavioral outcomes.

Further longitudinal studies are urgently needed to characterize the natural history of pediatric neurological sequelae and to identify interventions capable of mitigating long-term developmental consequences.

Integrated Model of Ebola Neuropathogenesis

Current evidence supports an integrated model in which neurological injury arises through multiple interacting pathways rather than a single pathogenic mechanism. Following systemic infection, extensive viral replication produces high circulating viral loads and widespread immune activation. Infected monocytes and macrophages disseminate throughout the body while simultaneously generating large quantities of inflammatory mediators.[26,39–41]

The resulting cytokine storm promotes endothelial dysfunction and disruption of blood-brain barrier integrity. Viral particles, inflammatory mediators, and infected immune cells subsequently gain access to neural tissues, where they activate resident microglia and astrocytes. This process initiates a self-amplifying cycle of neuroinflammation characterized by cytokine production, oxidative stress, excitotoxicity, and neuronal dysfunction.[17,24,26,34]

Concurrently, endothelial injury and coagulation abnormalities contribute to microvascular thrombosis, cerebral hypoperfusion, and hemorrhagic lesions. These vascular abnormalities further exacerbate neuronal injury and may account for focal neurological deficits and stroke-like syndromes observed in some patients.

Among survivors, persistent viral reservoirs within immune-privileged compartments may sustain chronic inflammatory responses and contribute to delayed neurological relapse. Ongoing neuroinflammation, combined with residual vascular injury and neuronal loss, likely underlies many of the chronic cognitive, psychiatric, and sensory symptoms reported years after recovery.[8,12,24,31]

Taken together, these observations support the concept that Ebola hemorrhagic fever encephalitis is a multifactorial neuroinfectious disorder characterized by complex interactions among viral replication, immune dysregulation, endothelial injury, vascular pathology, and persistent inflammation. Understanding these interactions will be essential

for developing future therapeutic strategies aimed at preventing both acute neurological injury and long-term neurological disability.

Clinical Presentations of Ebola Hemorrhagic Fever Encephalitis

The clinical manifestations of Ebola hemorrhagic fever encephalitis encompass a broad spectrum of neurological abnormalities involving both the central and peripheral nervous systems. These manifestations may occur during acute infection, the convalescent phase, or many months after apparent recovery, reflecting the complex pathophysiological interactions among viral neuroinvasion, neuroinflammation, cerebrovascular injury, immune dysregulation, and persistent viral reservoirs.[7–13,24] The diversity of neurological presentations has become increasingly evident following the expansion of survivor cohorts and the availability of longitudinal follow-up studies, which have demonstrated that neurological complications contribute substantially to both acute morbidity and long-term disability.

Neurological manifestations may arise at any stage of Ebola virus disease. During acute infection, symptoms often occur in conjunction with systemic illness characterized by fever, gastrointestinal dysfunction, coagulopathy, and multiorgan involvement. In contrast, delayed neurological complications may emerge months or years after apparent recovery and frequently occur in the absence of active systemic disease. This temporal variability contributes significantly to diagnostic complexity and underscores the importance of maintaining long-term neurological surveillance among survivors.[8,9,12,24]

Acute Neurological Manifestations

Headache represents the most common neurological symptom during acute Ebola virus disease. It is frequently described as severe, diffuse, persistent, and poorly responsive to conventional analgesic therapy. Headaches often occur early in the disease course and may be accompanied by photophobia, dizziness, fatigue, and generalized malaise.[5,6,14,15] Although nonspecific, severe headache may represent one of the earliest indicators of CNS involvement and frequently precedes more overt neurological abnormalities.

Altered mental status is another prominent feature of severe infection. Patients may develop confusion, disorientation, impaired attention, agitation, fluctuating consciousness, and delirium. These manifestations often correlate with increasing disease severity and may reflect contributions from systemic inflammation, metabolic disturbances, cerebral hypoperfusion, neuroinflammation, and direct CNS involvement.[5,6,17] Delirium may present in hyperactive, hypoactive, or mixed forms and is frequently associated with poorer clinical outcomes.

As disease progresses, some patients develop profound encephalopathy characterized by severe cognitive dysfunction, reduced responsiveness, and progressive neurological deterioration. Distinguishing encephalopathy secondary to systemic illness from direct viral encephalitis may be challenging, particularly in resource-limited settings where neuroimaging and cerebrospinal fluid analysis are unavailable. Nevertheless, the occurrence of focal neurological deficits, seizures, meningeal signs, or persistent cognitive impairment should raise suspicion for direct CNS involvement.[17,24,25]

Ebola Encephalitis and Meningoencephalitis

Encephalitis represents one of the most severe neurological manifestations of Ebola virus disease. Patients may present with progressive confusion, behavioral changes, cognitive decline, seizures, focal neurological deficits, impaired

consciousness, and coma. The clinical course may be rapidly progressive and is frequently associated with extensive neuroinflammation and severe systemic disease.[8,9,24]

Meningoencephalitis has emerged as a particularly important complication following recognition of viral persistence within immune-privileged compartments. Patients typically present with severe headache, neck stiffness, photophobia, nausea, vomiting, altered mental status, and seizures. Cerebrospinal fluid analysis may demonstrate pleocytosis, elevated protein concentrations, inflammatory cytokines, and direct detection of Ebola viral RNA.[8,9,13,24]

The landmark case reported by Jacobs and colleagues dramatically altered understanding of Ebola neuropathogenesis. Approximately nine months after apparent recovery, a healthcare worker developed severe meningoencephalitis associated with detection of Ebola viral RNA within cerebrospinal fluid despite negative peripheral blood testing.[8] Subsequent reports from the Democratic Republic of Congo have documented additional cases of delayed meningoencephalitis, confirming that persistent CNS infection may result in recurrent neurological disease long after acute recovery.[12]

These observations suggest that Ebola encephalitis should not be viewed solely as an acute complication but rather as a potential manifestation of persistent viral infection capable of recurring months after systemic viral clearance.

Seizures and Epileptic Manifestations

Seizures constitute another important manifestation of Ebola-associated CNS disease. Both focal and generalized seizures have been reported during acute infection and may result from direct cortical injury, neuroinflammation, cerebral edema, vascular lesions, metabolic disturbances, or persistent CNS infection.[7–9,24]

Generalized tonic-clonic seizures appear to be the most frequently reported seizure type; however, focal seizures with or without secondary generalization have also been described. Because electroencephalography is rarely available during outbreaks, the true prevalence of epileptic activity remains unknown. It is likely that many patients with altered mental status experience unrecognized non-convulsive seizures or non-convulsive status epilepticus.[50,55]

Status epilepticus appears uncommon but has been documented in severe cases. The occurrence of recurrent seizures often indicates extensive neurological involvement and may be associated with poorer outcomes. Prompt recognition and treatment are therefore essential components of neurological management.

The long-term risk of epilepsy following Ebola encephalitis remains incompletely understood. Persistent cortical injury, gliosis, vascular abnormalities, and chronic neuroinflammation may theoretically contribute to epileptogenesis, although longitudinal studies addressing this question remain limited.[31,34]

Cerebrovascular Manifestations

Cerebrovascular complications have received increasing attention in recent years as understanding of Ebola-associated vascular pathology has expanded. Endothelial dysfunction, coagulopathy, disseminated intravascular coagulation, microvascular thrombosis, inflammatory vasculopathy, and hemorrhagic lesions collectively create conditions conducive to cerebrovascular injury.[26,39]

Patients may present with focal neurological deficits resembling ischemic stroke, including hemiparesis, facial weakness, aphasia, sensory abnormalities, visual disturbances, and gait dysfunction. In some cases, neuroimaging has revealed ischemic lesions, hemorrhagic abnormalities, or evidence of microvascular injury.[17,24]

The occurrence of stroke-like syndromes highlights the importance of vascular mechanisms in Ebola neuropathogenesis and reinforces the concept that neurological injury results from multiple overlapping pathological processes rather than direct viral infection alone.

Movement Disorders

Movement disorders represent increasingly recognized complications among Ebola survivors. Tremor is among the most frequently reported manifestations and may involve the upper extremities, lower extremities, head, or voice. Both resting and action tremors have been observed and may persist for years following recovery.[18–20,31]

Additional movement abnormalities include rigidity, bradykinesia, postural instability, impaired coordination, gait disturbances, and cerebellar dysfunction. These findings suggest involvement of basal ganglia, cerebellar pathways, and motor control networks. Persistent neuroinflammation, vascular injury, neuronal loss, and white matter abnormalities may contribute to the development of these disorders.

Although movement disorders are generally less common than cognitive or psychiatric symptoms, they can significantly impair mobility, independence, and quality of life. Rehabilitation and neurological follow-up therefore remain essential components of survivor care.

Cranial Nerve Dysfunction

Cranial neuropathies have been reported with increasing frequency among survivors of Ebola virus disease. Visual disturbances represent the most common manifestation and may result from optic nerve involvement, retinal injury, uveitis, or direct ocular infection.[23,31]

Affected individuals may experience blurred vision, photophobia, reduced visual acuity, floaters, visual field defects, or complete visual loss. The demonstration of persistent Ebola virus within ocular fluid has emphasized the importance of immune-privileged reservoirs and highlighted the close relationship between neurological and ophthalmological complications.[23]

Other cranial neuropathies include facial weakness, dysphagia, dysarthria, hearing impairment, tinnitus, vestibular dysfunction, and abnormalities of ocular motility. Although relatively uncommon, these manifestations provide further evidence of widespread neurological involvement.

Neuropsychiatric Presentations

Neuropsychiatric manifestations are among the most prevalent long-term consequences of Ebola virus disease. Depression, anxiety, emotional instability, post-traumatic stress disorder, sleep disturbances, chronic fatigue, and cognitive dysfunction occur at significantly higher rates among survivors than among uninfected populations.[18–20,31]

Patients frequently report persistent sadness, loss of motivation, emotional lability, excessive worry, social withdrawal, and impaired concentration. Such symptoms often coexist with chronic pain, fatigue, and cognitive deficits, creating complex clinical presentations that require multidisciplinary management.

The pathogenesis of neuropsychiatric symptoms is likely multifactorial and involves direct neurological injury, chronic neuroinflammation, altered neurotransmitter regulation, psychosocial trauma, social stigma, and economic disruption. Consequently, optimal management requires integration of neurological, psychiatric, psychological, and social support services.

Chronic Post-Ebola Neurological Syndrome

The term post-Ebola neurological syndrome has increasingly been used to describe the constellation of chronic neurological symptoms experienced by survivors following recovery from acute infection. This syndrome encompasses headaches, cognitive dysfunction, memory impairment, neuropathic pain, tremor, sleep disturbances, depression, anxiety, visual abnormalities, cranial neuropathies, and reduced quality of life.[18–20,31]

Longitudinal studies indicate that these manifestations may persist for many years and, in some cases, appear only after an initial period of recovery. The persistence of symptoms has prompted increasing concern regarding chronic neuroinflammation, ongoing immune activation, and residual structural injury within the nervous system.

Recognition of post-Ebola neurological syndrome has transformed survivor care by emphasizing the need for long-term neurological surveillance, rehabilitation services, neuropsychological assessment, and multidisciplinary clinical management.

Pediatric Neurological Presentations

Neurological complications among pediatric survivors remain incompletely characterized but are increasingly recognized as important contributors to long-term morbidity. Children may develop cognitive impairment, developmental delay, learning difficulties, behavioral abnormalities, emotional disturbances, and social dysfunction following infection.[29,69]

Because childhood represents a critical period for neurodevelopment, neurological injury occurring during Ebola infection may have lifelong consequences. Educational performance, psychosocial development, and future occupational opportunities may all be adversely affected. Long-term follow-up programs specifically targeting pediatric survivors are therefore urgently needed.

Collectively, the clinical manifestations of Ebola hemorrhagic fever encephalitis demonstrate that neurological involvement extends far beyond isolated episodes of acute encephalitis. Rather, Ebola virus disease encompasses a broad continuum of neurological injury involving cognitive, psychiatric, vascular, sensory, motor, and developmental domains. Recognition of this spectrum is essential for accurate diagnosis, effective management, and comprehensive survivor care.

The outbreaks and neurological presentations are shown below;

Table 4: Major Ebola Virus Disease Outbreaks and Reported Neurological Manifestations.

Outbreak	Year	Country/Region	Species	Cases	CFR (%)	Neurological Findings
Yambuku	1976	DRC	Zaire ebolavirus	318	88	Limited documentation due to high mortality
Sudan	1976	Sudan	Sudan ebolavirus	284	53	Headache, confusion
Kikwit	1995	DRC	Zaire ebolavirus	315	81	Delirium, altered consciousness
Uganda	2000–2001	Uganda	Sudan ebolavirus	425	53	Headache, encephalopathy
Bundibugyo	2007	Uganda	Bundibugyo ebolavirus	149	25	Limited neurological reporting
West Africa	2014–2016	Guinea, Liberia, Sierra Leone	Zaire ebolavirus	28,616	40	Encephalitis, seizures, cognitive dysfunction, neuropathic pain
Equateur	2018	DRC	Zaire ebolavirus	54	61	Neurocognitive sequelae reported
North Kivu	2018–2020	DRC	Zaire ebolavirus	3,481	66	Meningoencephalitis, delayed neurological relapse

Diagnosis and Diagnostic Dilemmas

The diagnosis of Ebola hemorrhagic fever encephalitis remains one of the most challenging aspects of managing neurological complications associated with Ebola virus disease. Although considerable advances have been made in molecular diagnostics, neuroimaging, and clinical surveillance during recent outbreaks, the identification of central nervous system involvement continues to be complicated by overlapping systemic manifestations, limited diagnostic resources in outbreak settings, and the evolving understanding of Ebola neuropathogenesis.[3,24,49,50,63] Consequently, diagnosis frequently requires integration of epidemiological exposure history, clinical findings, laboratory investigations, neuroimaging studies, cerebrospinal fluid analysis, and exclusion of competing neurological disorders.

A major diagnostic challenge arises from the fact that neurological manifestations often occur within the context of severe systemic illness. Patients with acute Ebola virus disease frequently develop fever, dehydration, electrolyte abnormalities, hepatic dysfunction, renal failure, hypoxemia, shock, and multiorgan dysfunction, each of which can independently produce altered mental status and neurological impairment.[2,3,24] As a result, clinicians must distinguish between encephalopathy secondary to systemic disease and direct viral involvement of the central nervous system.

The diagnosis of Ebola encephalitis should be considered whenever neurological symptoms develop in patients with confirmed or suspected Ebola virus disease. Clinical suspicion is particularly warranted in individuals presenting with severe headache, persistent confusion, behavioral changes, seizures, focal neurological deficits, neck stiffness, photophobia, altered consciousness, or unexplained cognitive deterioration.[7–10,24] Similarly, new neurological symptoms occurring months after apparent recovery should prompt evaluation for delayed neurological relapse associated with persistent CNS infection.[8,12,13]

A detailed clinical history represents the foundation of diagnostic assessment. Epidemiological risk factors remain critically important because they substantially influence pretest probability. Recent travel to areas experiencing active Ebola transmission, occupational exposure to infected patients, participation in burial practices, direct contact with infected bodily fluids, and exposure to potentially infected wildlife all increase the likelihood of Ebola virus

disease.[3,4,49,50] Among survivors, previous laboratory-confirmed Ebola infection should immediately raise concern for delayed neurological complications when new neurological symptoms emerge.

Comprehensive neurological examination remains essential despite the diagnostic limitations frequently encountered during outbreaks. Assessment should include evaluation of consciousness, orientation, attention, memory, language function, cranial nerve integrity, motor strength, sensory function, coordination, gait, and reflexes. Particular attention should be directed toward identifying focal neurological deficits because such findings may suggest direct CNS involvement rather than generalized metabolic encephalopathy.[7,17,24]

Headache is among the most common neurological manifestations but lacks diagnostic specificity. However, severe or persistent headache accompanied by neck stiffness, photophobia, seizures, altered mental status, or focal neurological abnormalities may indicate meningeal or parenchymal CNS involvement. Similarly, progressive cognitive decline, personality changes, or behavioral disturbances should heighten suspicion for encephalitis.[8,9,24]

Laboratory confirmation of Ebola virus infection relies primarily on reverse transcriptase polymerase chain reaction (RT-PCR), which remains the diagnostic gold standard during acute disease.[62–64] RT-PCR enables highly sensitive detection of viral RNA in blood and other clinical specimens and has revolutionized outbreak management by facilitating rapid diagnosis and isolation of infected individuals. During acute infection, high viral loads detected by RT-PCR frequently correlate with disease severity and mortality risk.[43,65]

Despite its diagnostic value, peripheral blood RT-PCR possesses important limitations in the evaluation of Ebola encephalitis. Several landmark cases have demonstrated persistence of Ebola viral RNA within cerebrospinal fluid despite negative blood RT-PCR results.[8,12,13] These observations indicate that systemic viral clearance does not necessarily imply eradication of infection from immune-privileged CNS compartments. Consequently, negative blood testing cannot completely exclude ongoing neurological infection in symptomatic survivors.

Serological testing may provide supportive diagnostic information, particularly among individuals presenting with delayed neurological manifestations. Detection of Ebola-specific immunoglobulin G antibodies confirms prior exposure and may assist in establishing historical infection when documentation is unavailable.[49,52] However, serological assays cannot reliably distinguish active CNS infection from previous resolved disease and therefore should be interpreted within the broader clinical context.

Cerebrospinal fluid analysis represents one of the most informative investigations for evaluating suspected Ebola encephalitis. Lumbar puncture may reveal lymphocytic pleocytosis, elevated protein concentrations, increased inflammatory cytokines, and direct detection of Ebola viral RNA.[8,9,13,24] The identification of viral RNA within cerebrospinal fluid provides compelling evidence of direct CNS involvement and has been central to establishing the concept of persistent Ebola meningoencephalitis.

Nevertheless, lumbar puncture presents several challenges during Ebola outbreaks. Biosafety concerns, coagulopathy, thrombocytopenia, hemodynamic instability, and limited laboratory infrastructure often restrict access to cerebrospinal fluid analysis. In many outbreak settings, lumbar puncture may be considered unsafe or impractical, thereby limiting diagnostic certainty. Consequently, many cases of suspected Ebola encephalitis are diagnosed on clinical grounds rather than direct laboratory confirmation.

Neuroimaging plays an increasingly important role in the evaluation of neurological complications. Computed tomography may demonstrate cerebral edema, intracranial hemorrhage, hydrocephalus, ischemic lesions, or mass effect. However, CT possesses limited sensitivity for detecting early inflammatory changes and subtle encephalitic lesions.[24,55]

Magnetic resonance imaging provides superior characterization of CNS pathology and may reveal meningeal enhancement, white matter abnormalities, inflammatory lesions, cerebral edema, ventricular involvement, and evidence of encephalitis. MRI may also assist in excluding alternative diagnoses such as stroke, abscess, neoplasm, or demyelinating disease. Unfortunately, MRI availability remains severely limited in many regions where Ebola outbreaks occur, restricting its utility as a routine diagnostic modality.[55]

Electroencephalography may provide valuable information regarding cerebral dysfunction and seizure activity. Generalized slowing, focal abnormalities, epileptiform discharges, and non-convulsive status epilepticus may be detected in affected patients. Because many critically ill individuals experience altered consciousness without overt convulsive activity, EEG monitoring may identify clinically unrecognized seizures contributing to neurological deterioration.[55,66] However, continuous EEG monitoring is rarely available in outbreak settings.

One of the most important diagnostic dilemmas involves differentiating Ebola encephalitis from systemic encephalopathy. Severe Ebola virus disease frequently produces metabolic disturbances capable of causing profound neurological dysfunction independent of direct CNS infection. Hypoglycemia, electrolyte abnormalities, hepatic failure, renal dysfunction, hypoxemia, septic shock, and cytokine-mediated systemic inflammation may all impair cerebral function.[2,24,55] Consequently, altered mental status alone cannot be considered diagnostic of encephalitis.

The differential diagnosis is particularly challenging in endemic regions where numerous infectious diseases coexist. Cerebral malaria remains one of the most important alternative diagnoses because it commonly presents with fever, seizures, altered consciousness, and coma.[57] Similarly, bacterial meningitis, tuberculous meningitis, herpes simplex encephalitis, arboviral infections, human African trypanosomiasis, and Lassa fever may closely mimic Ebola-associated neurological disease.[63,67–70]

Autoimmune and postinfectious inflammatory disorders further complicate diagnostic assessment. Conditions such as acute disseminated encephalomyelitis, autoimmune encephalitis, and postinfectious demyelinating syndromes may produce neurological symptoms resembling those associated with persistent Ebola infection.[71,72] Distinguishing these disorders often requires specialized testing that may not be readily available in resource-limited settings.

Delayed neurological relapse presents an additional diagnostic challenge. The recognition of persistent viral reservoirs within immune-privileged CNS compartments has fundamentally altered traditional assumptions regarding recovery from Ebola virus disease.[8,12,24] Survivors presenting months after apparent recovery with headache, cognitive decline, seizures, or altered consciousness may harbor persistent CNS infection despite negative peripheral blood testing. Failure to recognize this phenomenon may result in diagnostic delay and inappropriate management.

Recent advances in molecular diagnostics offer promising opportunities for improving diagnostic accuracy. High-sensitivity RT-PCR assays, next-generation sequencing technologies, multiplex pathogen detection platforms, and emerging biomarker-based approaches may facilitate earlier recognition of CNS involvement.[62–64] Likewise,

investigation of biomarkers such as neurofilament light chain, glial fibrillary acidic protein, inflammatory cytokines, and endothelial injury markers may improve detection of neurological injury and assist in prognostic stratification.[56,82]

Artificial intelligence and machine learning approaches may also contribute to future diagnostic frameworks. Predictive models integrating epidemiological data, clinical findings, laboratory results, imaging characteristics, and biomarker profiles could potentially identify patients at greatest risk for neurological complications and facilitate earlier intervention.

Ultimately, the diagnosis of Ebola hemorrhagic fever encephalitis requires a multidisciplinary approach involving infectious disease specialists, neurologists, neuroradiologists, intensivists, laboratory scientists, and public health professionals. Given the substantial overlap between systemic illness and direct neurological infection, clinicians must maintain a high index of suspicion and integrate multiple sources of information when evaluating affected patients. Continued improvements in diagnostic infrastructure, molecular technologies, neuroimaging capabilities, and standardized case definitions will be essential for advancing recognition and management of Ebola-associated CNS disease. The diagnostic algorithm is described below;

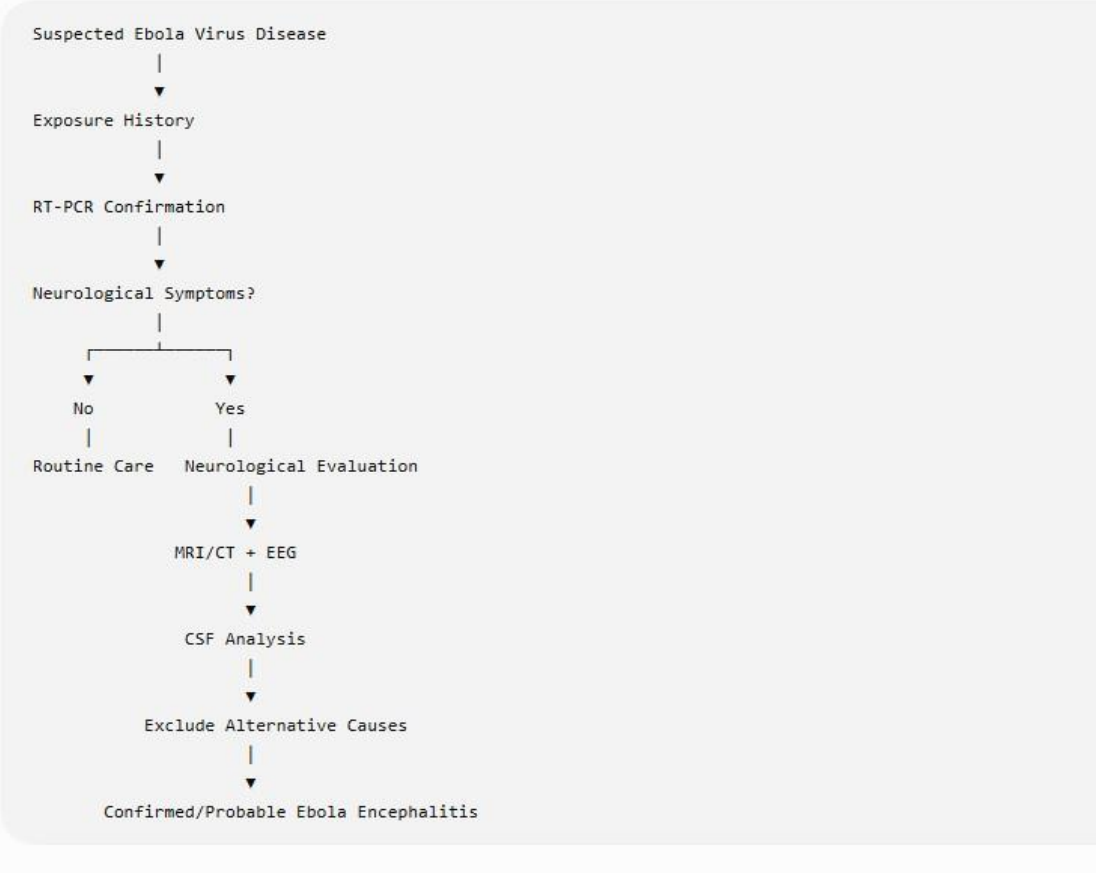

Figure 4: Diagnostic Algorithm for Ebola Hemorrhagic Fever Encephalitis.

Differential Diagnoses

The differential diagnosis of Ebola hemorrhagic fever encephalitis is extensive and reflects the nonspecific nature of many neurological manifestations associated with severe infectious diseases. Accurate differentiation is particularly important because numerous alternative conditions require fundamentally different therapeutic approaches and may

coexist with Ebola virus disease in endemic regions. Moreover, many disorders share common clinical features, including fever, altered mental status, seizures, focal neurological deficits, and meningeal irritation, thereby creating substantial diagnostic overlap. One of the most important differential considerations is cerebral malaria. The differential diagnoses are shown below;

Table 5: Differential Diagnoses of Ebola Hemorrhagic Fever Encephalitis.

Condition	Distinguishing Features
Cerebral malaria	Positive malaria smear, parasitemia
Bacterial meningitis	Neutrophilic CSF, low glucose
Tuberculous meningitis	Chronic course, basilar enhancement
HSV encephalitis	Temporal lobe MRI abnormalities
Japanese encephalitis	Mosquito exposure history
West Nile encephalitis	Flaccid paralysis may occur
Lassa fever	Sensorineural hearing loss
Marburg virus disease	Requires molecular differentiation
Autoimmune encephalitis	Autoantibodies present
ADEM	Multifocal demyelinating lesions

Treatment and Treatment Algorithms

The management of Ebola hemorrhagic fever encephalitis requires a comprehensive, multidisciplinary approach that simultaneously addresses systemic Ebola virus disease, acute neurological complications, and long-term neurological sequelae. Unlike several viral encephalitides for which pathogen-specific neurotherapeutic interventions exist, no treatment has been developed specifically for Ebola-associated encephalitis. Consequently, current management strategies rely upon a combination of antiviral therapy, intensive supportive care, neurocritical care interventions, seizure management, rehabilitation services, and long-term neurological surveillance.[21,24,52,53,78,79]

Successful treatment begins with early recognition of neurological involvement. Delays in diagnosis may permit progression of neuroinflammation, cerebral edema, seizure activity, and systemic complications that contribute to both mortality and long-term neurological disability. Therefore, clinicians caring for patients with confirmed or suspected Ebola virus disease should maintain a high index of suspicion whenever neurological symptoms emerge.

The initial management of patients presenting with suspected Ebola encephalitis follows the fundamental principles of emergency stabilization. Airway protection, respiratory support, circulatory stabilization, and infection-control measures remain immediate priorities. Patients with altered consciousness, recurrent seizures, severe encephalopathy, or evidence of meningoencephalitis frequently require intensive care unit admission and continuous physiological monitoring.[24,53]

Maintenance of adequate oxygenation and cerebral perfusion is particularly important because secondary neurological injury may result from hypoxemia, hypotension, shock, and metabolic disturbances. Aggressive management of dehydration remains essential because severe gastrointestinal fluid losses frequently contribute to hypovolemia and impaired cerebral blood flow. Intravenous fluid resuscitation must be carefully balanced to maintain adequate organ perfusion while minimizing the risk of worsening cerebral edema in patients with significant CNS involvement.[14,15,24]

Electrolyte abnormalities require prompt correction because disturbances in sodium, potassium, calcium, magnesium, and glucose homeostasis may exacerbate encephalopathy and lower seizure thresholds. Hypoglycemia, which may occur in critically ill patients with Ebola virus disease, can independently produce severe neurological dysfunction and

must be rapidly identified and corrected. Similarly, hepatic and renal dysfunction should be aggressively managed because accumulation of metabolic toxins may contribute substantially to neurological deterioration.[24,53,55]

A major therapeutic advance occurred during the 2018–2020 Ebola outbreak in the Democratic Republic of Congo through the PALM (Pamoja Tulinde Maisha) trial. This landmark randomized controlled study demonstrated that monoclonal antibody therapies significantly improved survival among patients infected with *Zaire ebolavirus.*[21] Ansuvimab (Ebanga) and the triple monoclonal antibody combination atoltivimab, maftivimab, and odesivimab-ebgn (Inmazeb) were associated with substantially lower mortality compared with earlier investigational therapies and subsequently became recommended treatments for confirmed *Zaire ebolavirus* infection.[21,78,79]

Although these therapies were developed primarily to reduce systemic viral replication, they may also have important neurological implications. Early suppression of viral replication could theoretically reduce neuroinvasion, limit blood-brain barrier injury, decrease cytokine-mediated neuroinflammation, and diminish the likelihood of persistent viral reservoirs within immune-privileged compartments. However, direct evidence regarding their effects on neurological outcomes remains limited and represents an important area for future investigation.

Historically, several investigational antiviral therapies were evaluated during Ebola outbreaks. Favipiravir, brincidofovir, TKM-130803, ZMapp, remdesivir, and other agents demonstrated varying degrees of efficacy and feasibility.[44–46] Although these therapies contributed significantly to understanding Ebola treatment, current evidence supports monoclonal antibody therapy as the preferred approach for acute *Zaire ebolavirus* infection. The treatment algorithm is described below;

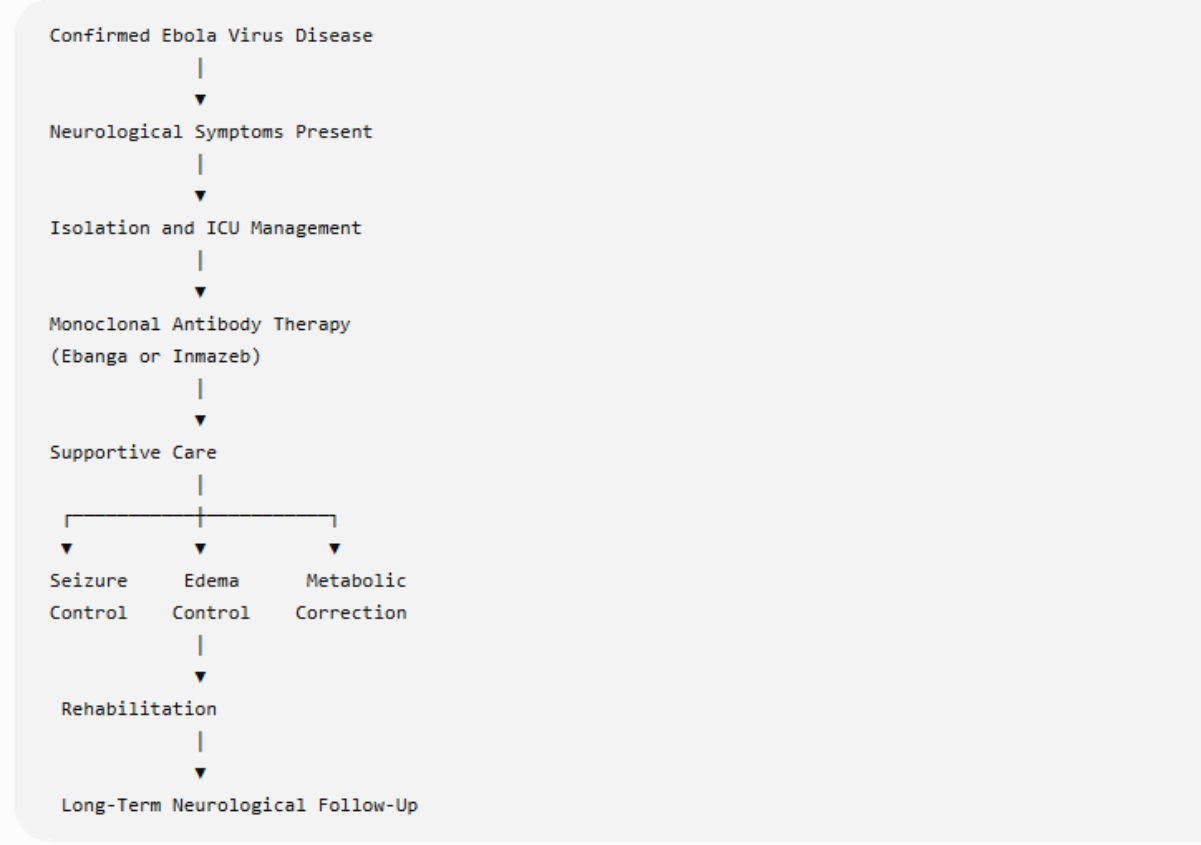

Figure 6: Treatment Algorithm.

Management of seizures represents a critical component of neurological care. Acute seizures should be treated promptly according to established neurocritical care protocols. Benzodiazepines remain first-line agents for seizure termination because of their rapid onset of action and effectiveness in controlling both focal and generalized seizures. Lorazepam, diazepam, and midazolam are commonly employed depending on availability and clinical circumstances.

Following stabilization, longer-term antiseizure therapy may be required in patients experiencing recurrent seizures or evidence of cortical injury. Levetiracetam is often favored because of its favorable safety profile, minimal drug-drug interactions, and ease of administration. Valproic acid, lacosamide, and other antiseizure medications may also be considered depending on individual patient characteristics and resource availability. Continuous electroencephalographic monitoring would be ideal in patients with persistent altered consciousness because non-convulsive seizures may otherwise remain undetected.[55,66]

Patients with status epilepticus require aggressive management because prolonged seizure activity may contribute to irreversible neuronal injury and increased mortality. Treatment follows conventional neurocritical care algorithms involving escalating antiseizure therapy, airway protection, and intensive monitoring. Resource limitations frequently complicate management in outbreak settings, underscoring the need for improved neurological infrastructure in regions at risk for Ebola epidemics.

Cerebral edema represents another important therapeutic challenge. Although the precise incidence of elevated intracranial pressure during Ebola encephalitis remains unknown, available neuropathological and neuroimaging studies indicate that cerebral swelling may contribute to neurological deterioration.[17,27,39] Management includes head-of-bed elevation, optimization of oxygenation, maintenance of normoglycemia, avoidance of hyperthermia, and correction of metabolic abnormalities. Osmotherapy may be considered in selected cases, although evidence specific to Ebola encephalitis remains limited.

Neuroinflammation represents a potentially important therapeutic target. However, the role of immunomodulatory therapy remains uncertain. Excessive inflammation contributes substantially to tissue injury, yet suppression of immune responses may theoretically impair viral clearance. Consequently, corticosteroids and other immunosuppressive therapies should be used cautiously and only when specific indications exist. Future research examining targeted modulation of inflammatory pathways may identify safer and more effective approaches to reducing neurological injury.

Management of cerebrovascular complications requires individualized assessment. Patients presenting with ischemic stroke-like syndromes, hemorrhagic lesions, or severe coagulopathy often require complex multidisciplinary care involving neurologists, intensivists, hematologists, and infectious disease specialists. Standard stroke management protocols may require modification because of the unique coagulation abnormalities associated with Ebola virus disease.

The treatment of delayed neurological relapse associated with persistent CNS infection remains particularly challenging. Several case reports have documented successful management using combinations of antiviral therapy, monoclonal antibodies, intensive supportive care, and neurological monitoring.[8,12,24] However, standardized treatment guidelines have not yet been established because of the rarity of these presentations and the limited available evidence.

The increasing recognition of persistent viral reservoirs within immune-privileged compartments has prompted growing interest in therapies capable of penetrating the CNS and eliminating residual infection. Future therapeutic development may focus on agents specifically designed to target persistent viral reservoirs while minimizing neurotoxicity and preserving normal immune function.

Rehabilitation represents an essential but frequently underappreciated component of treatment. Many survivors experience persistent neurological deficits that significantly impair functional independence and quality of life. Comprehensive rehabilitation programs incorporating physical therapy, occupational therapy, speech-language therapy, neuropsychological assessment, cognitive rehabilitation, and psychiatric support have demonstrated substantial benefits among survivors.[18–20,31]

Physical rehabilitation focuses on restoring strength, balance, mobility, coordination, and endurance. Occupational therapy assists survivors in regaining independence in daily activities, while cognitive rehabilitation addresses deficits in memory, attention, executive function, and problem-solving. Speech and language therapy may be required in patients experiencing communication difficulties, cranial neuropathies, or cognitive-linguistic impairment.

Psychiatric and psychological support remain equally important. Depression, anxiety, post-traumatic stress disorder, sleep disturbances, and chronic fatigue frequently complicate recovery and may significantly impair long-term outcomes. Integrated mental health services should therefore be considered a routine component of survivor care rather than an optional adjunct.

Long-term follow-up constitutes the final stage of management. Survivors should undergo periodic neurological evaluations to identify persistent symptoms, monitor cognitive function, assess psychiatric wellbeing, and detect evidence of delayed CNS relapse. Given the potential for viral persistence within immune-privileged compartments, continued surveillance remains warranted even after apparent clinical recovery.[8,12,24]

A practical treatment algorithm begins with recognition of neurological symptoms in a patient with confirmed or suspected Ebola virus disease. Following implementation of infection-control precautions and stabilization of airway, breathing, and circulation, laboratory confirmation should be pursued using RT-PCR and other available diagnostic modalities. Neurological assessment should include detailed examination, neuroimaging when feasible, cerebrospinal fluid analysis when safe, and electroencephalographic evaluation when available. Antiviral therapy should be initiated promptly, while supportive care addresses seizures, metabolic disturbances, cerebral edema, cerebrovascular complications, and systemic illness. Survivors should subsequently enter structured rehabilitation and long-term surveillance programs designed to optimize neurological recovery and identify late complications.

Collectively, current evidence suggests that successful management of Ebola hemorrhagic fever encephalitis requires early diagnosis, prompt antiviral therapy, meticulous supportive care, aggressive management of neurological complications, comprehensive rehabilitation, and sustained long-term follow-up. As understanding of Ebola neuropathogenesis continues to evolve, future therapeutic strategies will likely increasingly target neuroinflammation, viral persistence, endothelial dysfunction, and chronic neurological disability.

Prognosis

The prognosis of Ebola hemorrhagic fever encephalitis is highly variable and depends upon the severity of systemic infection, extent of neurological involvement, viral burden, timing of diagnosis, availability of antiviral therapy, access to intensive care resources, and the development of long-term neurological sequelae. Historically, neurological manifestations occurring during Ebola virus disease were associated with particularly poor outcomes because they frequently reflected severe systemic illness, extensive inflammatory injury, and multiorgan dysfunction.[2,5,14]

Prior to the availability of modern supportive care and monoclonal antibody therapies, mortality rates among patients with severe Ebola virus disease often exceeded 70% in many outbreak settings.[2,4,60] Patients presenting with profound encephalopathy, seizures, coma, or meningoencephalitis generally exhibited especially poor prognoses because these manifestations frequently occurred in association with advanced disease and high circulating viral loads.

The prognosis of Ebola hemorrhagic fever encephalitis has improved substantially during the past decade because of advances in outbreak management, earlier diagnosis, improved supportive care, and the introduction of monoclonal antibody therapies. Nevertheless, neurological involvement remains an important predictor of morbidity and, in many cases, mortality. Patients who develop severe encephalitis, recurrent seizures, meningoencephalitis, coma, or extensive neuroinflammatory injury frequently experience more complicated clinical courses than those without neurological manifestations.[7–9,24]

Several factors appear to influence short-term outcomes. Viral load remains among the most important prognostic indicators. Studies conducted during the West African epidemic demonstrated that elevated viral RNA levels at presentation were strongly associated with disease severity and mortality.[43,65] Patients with high viral burdens are more likely to develop systemic inflammatory dysregulation, endothelial dysfunction, multiorgan failure, and neurological complications. Consequently, viral burden may indirectly influence neurological prognosis through its effects on disease severity and host inflammatory responses.

Age also appears to influence outcomes. Young children and older adults generally exhibit higher mortality rates than healthy young adults. Among pediatric survivors, neurological injury may have particularly profound long-term consequences because infection occurs during critical periods of neurodevelopment. Cognitive impairment, developmental delay, educational difficulties, and psychosocial dysfunction may persist for years and influence adult functioning.[29,69]

The timing of therapeutic intervention significantly affects prognosis. Early initiation of effective antiviral therapy, particularly monoclonal antibody treatment, has been associated with improved survival among patients with *Zaire ebolavirus* infection.[21,78,79] Although direct evidence linking early antiviral therapy to improved neurological outcomes remains limited, it is biologically plausible that early suppression of viral replication reduces neuroinvasion, blood-brain barrier injury, and neuroinflammatory damage.

The severity of neurological involvement itself represents a major determinant of outcome. Patients presenting with mild neurological symptoms such as headache or transient confusion frequently recover without major disability. In contrast, those who develop severe encephalitis, prolonged seizures, focal neurological deficits, persistent

meningoencephalitis, or delayed neurological relapse are more likely to experience residual neurological impairment.[8,9,12,24]

One of the most important developments in understanding prognosis has been the recognition that survival does not necessarily equate with complete recovery. Increasing numbers of survivors experience chronic neurological, neuropsychiatric, and cognitive sequelae that substantially affect quality of life.[18–20,31] Consequently, prognosis should be viewed as a multidimensional concept encompassing survival, neurological recovery, cognitive function, psychological wellbeing, social reintegration, and long-term functional independence.

Headaches represent one of the most persistent symptoms reported among survivors and may continue for years following infection. Although rarely life-threatening, chronic headaches contribute substantially to reduced quality of life and healthcare utilization. Similarly, cognitive dysfunction may impair educational attainment, occupational performance, and independent living, thereby creating long-term socioeconomic consequences for affected individuals and their communities.[18–20,31]

Neuropsychiatric manifestations further complicate prognosis. Depression, anxiety disorders, post-traumatic stress disorder, sleep disturbances, and chronic fatigue frequently persist after recovery and may be as disabling as physical neurological deficits. These conditions often interact with cognitive impairment and chronic pain syndromes, creating complex clinical presentations that require multidisciplinary management.[18–20,31]

Persistent viral reservoirs introduce an additional dimension to prognosis. The demonstration of Ebola viral persistence within cerebrospinal fluid and other immune-privileged compartments indicates that some survivors remain at risk for delayed neurological relapse long after apparent recovery.[8,12,24] Although such events appear relatively uncommon, their occurrence challenges traditional concepts of convalescence and necessitates prolonged clinical surveillance.

Several survivor studies have provided valuable insights into long-term outcomes. The PREVAIL III cohort demonstrated that many neurological symptoms gradually improve over time; however, a substantial proportion of survivors continue to experience persistent deficits years after infection.[14,31] Similar findings have been reported from Sierra Leone, Guinea, and the Democratic Republic of Congo, suggesting that chronic neurological morbidity represents a consistent feature of Ebola survivorship rather than an isolated phenomenon.[18–20]

The prognosis of visual complications deserves particular attention. Ocular involvement, including uveitis and retinal pathology, may result in severe visual impairment or blindness if not promptly recognized and treated.[23] Because visual dysfunction significantly affects independence and quality of life, early ophthalmological evaluation should form part of comprehensive survivor care.

Motor abnormalities such as tremor, gait dysfunction, weakness, and impaired coordination generally exhibit variable outcomes. Some survivors experience gradual improvement with rehabilitation, whereas others continue to demonstrate persistent disability. The extent of structural neurological injury, neuroinflammation, and rehabilitation access likely influences recovery trajectories.[18–20]

Quality-of-life assessments consistently demonstrate reduced wellbeing among survivors with persistent neurological symptoms. Difficulties returning to work, educational disruption, social isolation, stigma, and chronic healthcare needs

contribute to long-term burden. These findings emphasize that successful management extends beyond survival and requires attention to the broader social and functional consequences of neurological disease.

Emerging evidence suggests that multidisciplinary rehabilitation programs can significantly improve outcomes. Physical therapy, occupational therapy, cognitive rehabilitation, psychiatric support, social services, and structured survivor clinics have all been associated with improved functional recovery and quality of life.[18–20,31] Consequently, access to rehabilitation services represents an important prognostic determinant that may be modifiable through healthcare policy and resource allocation.

Overall, the prognosis of Ebola hemorrhagic fever encephalitis has improved substantially because of advances in supportive care and antiviral therapy. Nevertheless, neurological complications remain important contributors to mortality, disability, and reduced quality of life. Continued research into predictors of outcome, mechanisms of persistent neurological injury, and effective rehabilitation strategies will be essential for improving long-term prognosis among survivors.

The long term sequalae is shown below;

Table 6: Long-Term Neurological Sequelae Among Ebola Survivors.

Manifestation	Reported Frequency
Headache	Very common
Cognitive dysfunction	Common
Memory impairment	Common
Depression	Common
Anxiety	Common
Tremor	Moderate
Neuropathic pain	Common
Sleep disorders	Common
Visual disturbances	Common
Cranial neuropathies	Less common
Gait instability	Moderate
Persistent seizures	Rare

DISCUSSION

The neurological dimensions of Ebola virus disease have emerged as one of the most important developments in contemporary filovirus research. Historically, Ebola virus disease was viewed primarily as an acute viral hemorrhagic fever characterized by fever, gastrointestinal dysfunction, coagulopathy, endothelial injury, shock, and multiorgan failure.[2,3] Although neurological symptoms were occasionally described during earlier outbreaks, they were generally regarded as secondary consequences of severe systemic illness rather than manifestations of direct nervous system involvement.

The unprecedented West African epidemic fundamentally transformed this perspective. The survival of thousands of individuals created an opportunity to study the long-term consequences of infection in ways that had not previously been possible. As survivor cohorts expanded and longitudinal follow-up studies were established, it became increasingly evident that neurological complications were both common and clinically significant.[14,18–20,31] This realization prompted a paradigm shift in understanding Ebola virus disease, from a purely systemic hemorrhagic illness to a disorder capable of producing acute and chronic neurological injury.

One of the most compelling findings emerging from recent investigations is the demonstration that Ebola virus possesses genuine neuroinvasive potential. Multiple clinical reports have documented direct evidence of central nervous system infection, including detection of Ebola viral RNA within cerebrospinal fluid, delayed meningoencephalitis, and persistent CNS viral reservoirs.[8,9,12,13,24] These observations provide strong support for the concept that Ebola virus can establish infection within neural tissues rather than merely producing indirect neurological effects through systemic illness.

The recognition of persistent CNS reservoirs has particularly profound implications. Traditionally, recovery from viral infection has been equated with clearance of detectable virus from peripheral blood. However, cases of delayed meningoencephalitis occurring months after apparent recovery demonstrate that immune-privileged compartments may harbor persistent infection despite negative systemic testing.[8,12,24] This phenomenon fundamentally challenges conventional assumptions regarding viral clearance and raises important questions concerning surveillance, treatment, and long-term management.

Current evidence suggests that neurological injury results from a complex interaction among multiple pathogenic mechanisms. Direct viral neuroinvasion likely contributes to tissue injury in some patients. Simultaneously, extensive neuroinflammation, endothelial dysfunction, blood-brain barrier disruption, microvascular thrombosis, cytokine-mediated toxicity, and immune dysregulation collectively amplify neurological damage.[17,24–27,34] This multifactorial model helps explain the remarkable diversity of clinical manifestations observed across the disease spectrum.

The role of neuroinflammation deserves particular emphasis. Severe Ebola virus disease is characterized by profound cytokine activation and immune dysregulation. While inflammatory responses are essential for viral control, excessive activation may become pathological and contribute substantially to neurological injury. Persistent neuroinflammation may also explain why many survivors continue to experience cognitive dysfunction, psychiatric symptoms, headaches, and chronic pain despite apparent virological recovery.

Another important theme emerging from the literature is the substantial burden of chronic neurological disease among survivors. Headaches, cognitive impairment, depression, anxiety, sleep disturbances, tremor, neuropathic pain, visual abnormalities, and reduced quality of life have been reported consistently across multiple survivor cohorts.[18–20,31] These findings indicate that Ebola virus disease should not be viewed solely as an acute infectious illness but rather as a condition capable of producing chronic neurological disability.

The public health implications of these observations are substantial. In heavily affected regions, neurological sequelae may persist long after outbreaks have ended, creating ongoing healthcare needs and socioeconomic challenges. Survivors may require long-term neurological care, rehabilitation services, mental health support, educational assistance, and social reintegration programs. Consequently, outbreak recovery efforts must extend beyond transmission control and mortality reduction to address the enduring neurological consequences of infection.

Furthermore, the study of Ebola encephalitis provides broader insights into viral neurobiology. The mechanisms underlying CNS invasion, immune evasion, persistent infection, and chronic neuroinflammation may have relevance for numerous other neurotropic pathogens. Thus, advances in understanding Ebola neuropathogenesis may inform future research involving emerging viral diseases and pandemic preparedness.

Limitations

Despite substantial advances in understanding the neurological manifestations of Ebola virus disease, important limitations continue to affect the current body of evidence regarding Ebola hemorrhagic fever encephalitis. These limitations arise from methodological challenges, outbreak-related constraints, restricted access to advanced neurological investigations, and the relative rarity of comprehensive neuropathological studies.

One of the most significant limitations is the scarcity of prospective neurological investigations conducted during active outbreaks. Much of the available literature consists of case reports, retrospective analyses, observational studies, and survivor cohort investigations. Although these studies have provided valuable insights into neurological complications, they frequently lack standardized neurological assessments, uniform diagnostic criteria, and systematic long-term follow-up (7–13,18–20). Consequently, the true incidence and prevalence of Ebola-associated encephalitis remain incompletely defined.

Diagnostic limitations have also contributed substantially to gaps in knowledge. Many Ebola outbreaks occur in regions with limited access to advanced neuroimaging, electroencephalography, cerebrospinal fluid analysis, neuropsychological testing, and neuropathological services. As a result, numerous cases of neurological involvement may remain unrecognized or be incorrectly attributed to systemic encephalopathy secondary to multiorgan dysfunction. The distinction between direct viral encephalitis and indirect neurological injury therefore remains difficult in many patients.[24,55,63]

Another important limitation involves the relatively small number of confirmed cases of persistent CNS infection. Although landmark reports have demonstrated Ebola viral persistence within cerebrospinal fluid and have fundamentally altered understanding of Ebola neuropathogenesis, the rarity of documented cases limits the ability to determine the true frequency, risk factors, and long-term consequences of persistent infection.[8,12,13,24] It remains possible that persistent CNS reservoirs occur more frequently than currently recognized but remain undiagnosed because of inadequate surveillance and diagnostic resources.

Neuropathological evidence remains particularly limited. Biosafety concerns, cultural practices, logistical challenges, and restricted access to high-containment laboratory facilities have significantly constrained postmortem investigations. Consequently, many aspects of Ebola neuropathology continue to rely on animal models and isolated human case reports rather than large-scale pathological studies.[17,27,39] Further neuropathological investigations are necessary to clarify the precise anatomical distribution and cellular targets of CNS infection.

The heterogeneity of survivor studies presents an additional challenge. Differences in study design, patient populations, outcome measures, duration of follow-up, and definitions of neurological sequelae make direct comparisons difficult. Reported prevalence rates for cognitive dysfunction, psychiatric symptoms, headaches, and other neurological manifestations vary considerably among studies, reflecting methodological differences as well as genuine biological variability.[18–20,31]

Potential confounding by psychosocial factors must also be acknowledged. Survivors frequently experience bereavement, social stigma, economic hardship, educational disruption, and psychological trauma. These factors may independently contribute to cognitive impairment, depression, anxiety, sleep disturbances, and reduced quality of life.

Distinguishing direct neurological injury from secondary psychosocial consequences therefore remains challenging in many investigations.[18–20]

Most available evidence derives from outbreaks involving *Zaire ebolavirus*, particularly the 2014–2016 West African epidemic and subsequent outbreaks in the Democratic Republic of Congo. Comparatively little information is available regarding neurological manifestations associated with *Sudan ebolavirus*, *Bundibugyo ebolavirus*, or other species. Consequently, current understanding may not be fully generalizable across all Ebola virus species.[1,29]

Finally, the long-term neurological trajectory of survivors remains incompletely characterized. Although several studies have documented persistent symptoms extending for years after infection, relatively few cohorts have undergone follow-up beyond a decade. The possibility of progressive neurological decline, late neurodegenerative consequences, or delayed relapse therefore cannot be completely excluded.

Future Directions

The growing recognition of Ebola hemorrhagic fever encephalitis highlights numerous opportunities for future research. Continued investigation will be essential for improving understanding of neuropathogenesis, enhancing diagnostic accuracy, developing targeted therapies, and optimizing long-term survivor care.

One of the highest research priorities involves elucidating the precise mechanisms by which Ebola virus enters and persists within the central nervous system. Although current evidence supports hematogenous dissemination, blood-brain barrier disruption, and immune-cell-mediated transport, the molecular pathways governing neuroinvasion remain incompletely understood.[24–27,34] Identification of these mechanisms may facilitate development of therapeutic interventions capable of preventing CNS infection.

Further investigation of persistent viral reservoirs is particularly important. The discovery of Ebola viral persistence within cerebrospinal fluid and other immune-privileged compartments represents one of the most significant advances in Ebola research during the past decade.[8,12,24] Future studies should seek to determine the frequency of persistent infection, identify host and viral factors that promote persistence, and clarify the mechanisms underlying delayed neurological relapse.

Biomarker discovery represents another promising area of investigation. Reliable biomarkers capable of detecting early neurological injury, predicting long-term outcomes, identifying persistent infection, or monitoring treatment responses would substantially improve clinical management. Potential candidates include neurofilament light chain, glial fibrillary acidic protein, neuron-specific enolase, inflammatory cytokines, endothelial injury markers, and advanced neuroimaging biomarkers.[56,82]

Longitudinal neuroimaging studies are urgently needed. Magnetic resonance imaging, diffusion tensor imaging, functional MRI, positron emission tomography, and other advanced techniques may provide valuable insights into the structural and functional consequences of Ebola-associated neurological injury. Such investigations may clarify the relationship between imaging abnormalities and long-term clinical outcomes.

Future therapeutic development should extend beyond systemic viral suppression to address neurological injury directly. Although monoclonal antibody therapies have substantially improved survival, their effects on long-term

neurological outcomes remain uncertain.[21,78,79] Research focusing on neuroprotective therapies, anti-inflammatory interventions, endothelial stabilization, and elimination of persistent viral reservoirs may yield important advances.

Pediatric survivors deserve particular attention. Longitudinal investigations examining neurodevelopment, educational performance, psychosocial functioning, and adult neurological outcomes are needed to fully characterize the consequences of childhood Ebola infection. Such studies may identify opportunities for early intervention capable of mitigating lifelong disability.[29,69]

Artificial intelligence and machine learning technologies may further enhance future research efforts. Predictive models integrating clinical, laboratory, imaging, and genomic data could improve risk stratification and facilitate early identification of patients at greatest risk for neurological complications. Similarly, digital health platforms may enhance long-term monitoring of survivors in resource-limited settings.

International collaboration will remain essential for addressing these priorities. Establishment of multicenter survivor registries, standardized neurological assessment protocols, biorepositories, and coordinated research networks may accelerate scientific progress and improve the quality of available evidence.

Surveillance and Policy Recommendations

The recognition of neurological complications as major contributors to Ebola-related morbidity necessitates expansion of current surveillance frameworks. Historically, surveillance systems have focused primarily on transmission control, case detection, and mortality reduction. While these objectives remain critical, future surveillance programs must also address the long-term neurological consequences of infection.

Routine neurological assessment should be incorporated into Ebola treatment protocols and survivor follow-up programs. Standardized screening instruments evaluating cognitive function, mental health, motor performance, sensory abnormalities, sleep quality, and quality of life may facilitate earlier identification of neurological complications and improve access to rehabilitation services.[18–20,31]

Dedicated survivor clinics should be established in regions affected by Ebola outbreaks. These clinics should integrate neurology, infectious diseases, psychiatry, rehabilitation medicine, ophthalmology, social services, and primary care. Multidisciplinary care models have demonstrated substantial benefits in managing complex chronic sequelae and should become standard components of survivor care programs.

National public health agencies should develop surveillance systems specifically designed to monitor neurological outcomes. Standardized data collection regarding encephalitis, seizures, cognitive impairment, psychiatric disorders, movement abnormalities, cranial neuropathies, and delayed neurological relapse would provide valuable epidemiological information and facilitate future research.

Investment in diagnostic infrastructure is equally important. Expanded access to RT-PCR testing, neuroimaging, electroencephalography, cerebrospinal fluid analysis, neuropsychological assessment, and rehabilitation services would improve both patient care and scientific understanding. Strengthening healthcare systems in outbreak-prone regions would also enhance preparedness for future epidemics.

Healthcare worker education should emphasize recognition of neurological manifestations and the potential for delayed CNS relapse. Training programs should ensure that clinicians understand the spectrum of Ebola-associated neurological disease and maintain awareness of persistent viral reservoirs. Improved recognition may reduce diagnostic delays and improve outcomes.

Community engagement and survivor advocacy should be integrated into public health planning. Educational campaigns addressing stigma, misinformation, and barriers to healthcare access may facilitate earlier treatment-seeking behavior and improve long-term quality of life among survivors.

International organizations, including the World Health Organization, the Africa Centres for Disease Control and Prevention, and national ministries of health, should incorporate neurological outcomes into future Ebola preparedness frameworks. Such integration would ensure that neurological morbidity receives attention comparable to mortality and transmission control.

CONCLUSION

Ebola hemorrhagic fever encephalitis represents a severe and increasingly recognized neurological complication of Ebola virus disease. Contemporary evidence demonstrates that Ebola virus possesses significant neuroinvasive potential and may affect the central and peripheral nervous systems through a combination of direct viral infection, neuroinflammation, endothelial dysfunction, cerebrovascular injury, immune dysregulation, and persistent viral reservoirs within immune-privileged compartments.

Neurological manifestations span a broad clinical spectrum that includes headache, encephalopathy, encephalitis, meningoencephalitis, seizures, movement disorders, cranial neuropathies, cognitive dysfunction, psychiatric illness, and chronic post-Ebola neurological syndrome. Importantly, these complications may occur during acute infection, the convalescent phase, or many months after apparent recovery, highlighting the complex and dynamic nature of Ebola-associated neurological disease.

Advances in molecular diagnostics, neuroimaging, survivor research, and antiviral therapy have substantially improved understanding of Ebola neuropathogenesis. The demonstration of persistent viral infection within the CNS has fundamentally altered traditional concepts of viral clearance and recovery while emphasizing the need for prolonged neurological surveillance among survivors.

Although monoclonal antibody therapies have significantly improved survival, many survivors continue to experience substantial neurological morbidity. Consequently, successful management requires a comprehensive approach encompassing early diagnosis, effective antiviral therapy, neurocritical care, rehabilitation services, mental health support, and long-term follow-up.

Future progress will depend upon continued investigation of neuroinvasion mechanisms, persistent viral reservoirs, biomarkers of neurological injury, advanced therapeutic strategies, and survivor outcomes. Multidisciplinary collaboration among neurologists, infectious disease specialists, neuroscientists, epidemiologists, rehabilitation experts, and public health authorities will be essential for addressing the remaining gaps in knowledge.

The growing recognition of Ebola hemorrhagic fever encephalitis represents a paradigm shift in the understanding of Ebola virus disease. Historically, Ebola was primarily conceptualized as a fulminant viral hemorrhagic fever characterized by endothelial dysfunction, coagulopathy, immune dysregulation, and multiorgan failure.[2,3,26]

Neurological manifestations were generally considered secondary complications arising from severe systemic illness. However, evidence accumulated during and after the 2014–2016 West African epidemic has fundamentally challenged this traditional view and established the nervous system as a major target of Ebola virus-associated pathology.[7–13]

One of the most important contributions of recent investigations has been the demonstration that Ebola virus possesses genuine neuroinvasive capacity. The identification of viral RNA within cerebrospinal fluid, ocular fluid, and other immune-privileged compartments provided direct evidence that Ebola virus may persist beyond apparent systemic recovery.[8,9,12,13,23,24] These observations have important implications for understanding both acute disease pathogenesis and the chronic neurological complications increasingly recognized among survivors.

The concept of viral persistence has transformed thinking regarding recovery from Ebola virus disease. Historically, negative blood RT-PCR testing was considered evidence of viral clearance. However, cases of delayed meningoencephalitis occurring months after apparent recovery have demonstrated that the central nervous system may function as a reservoir capable of sustaining persistent infection despite negative peripheral testing.[8,12,24] Similar phenomena have been observed in other neurotropic viral infections, suggesting that immune-privileged compartments may play critical roles in long-term disease persistence.

The neuroinflammatory response appears central to Ebola neuropathogenesis. Excessive cytokine production contributes to blood-brain barrier disruption, endothelial dysfunction, microglial activation, astrocyte reactivity, and neuronal injury.[25–27,40,41] These inflammatory processes may persist beyond the period of active viral replication and potentially explain many chronic neurological manifestations observed among survivors. Persistent headaches, cognitive dysfunction, depression, anxiety, sleep disorders, and chronic fatigue may therefore represent the clinical consequences of sustained neuroimmune activation rather than ongoing direct viral injury alone.

Comparison with other viral encephalitides reveals both similarities and unique characteristics. Like herpes simplex encephalitis, Japanese encephalitis, and West Nile encephalitis, Ebola encephalitis may involve direct viral invasion of neural tissues and significant neuroinflammation.[65–68] However, Ebola differs in its profound systemic inflammatory response, extensive endothelial injury, and apparent capacity for long-term persistence within immune-privileged compartments. These distinctive features likely contribute to the unusually broad spectrum of neurological manifestations observed among survivors.

The neurological burden of Ebola virus disease also raises important questions regarding the relationship between infection and neurodegeneration. Although current evidence does not establish a direct link between Ebola infection and classical neurodegenerative disorders such as Alzheimer's disease or Parkinson's disease, persistent neuroinflammation is increasingly recognized as a potential driver of neurodegenerative processes. Longitudinal studies extending beyond ten years will therefore be essential for determining whether Ebola survivors experience increased risks of age-related neurodegenerative disease.

An additional issue deserving attention is the interaction between neurological disease and social determinants of health. Survivors often return to communities already facing substantial healthcare limitations, economic hardship, educational disruption, and social stigma. Persistent neurological symptoms may further reduce employability, educational attainment, and community participation, thereby amplifying existing socioeconomic vulnerabilities. Consequently, the burden of Ebola encephalitis extends far beyond clinical neurology and encompasses broader issues of public health, social justice, and health equity.

The increasing survival of patients with Ebola virus disease represents a major public health success. Nevertheless, improved survival has shifted the disease burden from mortality toward chronic disability. This epidemiological transition necessitates a corresponding shift in healthcare priorities. Future outbreak responses must extend beyond acute infection management to include long-term survivor care, neurological rehabilitation, mental health services, and structured surveillance programs.

Another important implication concerns outbreak preparedness. Traditional preparedness frameworks focus heavily on infection prevention, case identification, isolation, and mortality reduction. While these objectives remain essential, future preparedness efforts should also incorporate neurological expertise. Neurologists, neuropsychologists, rehabilitation specialists, psychiatrists, and neuroradiologists should be integrated into outbreak response teams to facilitate early recognition and management of neurological complications.

The emergence of effective monoclonal antibody therapies represents a transformative advance in Ebola management.[21,78,79] However, significant uncertainties remain regarding their neurological impact. It is currently unknown whether early antiviral therapy reduces CNS invasion, prevents persistent viral reservoirs, or decreases long-term neurocognitive complications. Future clinical trials should incorporate neurological endpoints to address these questions and guide evidence-based survivor care.

Finally, the study of Ebola encephalitis contributes to broader understanding of emerging infectious diseases. Recent outbreaks of Zika virus, SARS-CoV-2, Nipah virus, and monkeypox have highlighted the importance of neurological complications in emerging pathogens. Lessons learned from Ebola may therefore provide valuable insights applicable to future outbreaks and pandemic preparedness efforts. Understanding how viruses invade the nervous system, evade immune responses, persist within neural tissues, and produce chronic neurological disease remains one of the most important challenges in contemporary neuroinfectious disease research.

As survivor populations continue to expand, neurological complications are likely to become an increasingly important component of the global Ebola disease burden. Recognition of Ebola virus disease as both a systemic hemorrhagic fever and a neuroinfectious disorder provides a critical foundation for future research, clinical care, and public health preparedness. Comprehensive neurological surveillance, rehabilitation services, and survivor-centered healthcare models will be essential for reducing long-term disability and improving quality of life among affected individuals.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this work.

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Ethical Statement

This study is a descriptive narrative review based exclusively on previously published literature and publicly available data. Ethical approval and informed consent were not required because no human participants, patient identifiers, or primary clinical data were involved.

Data Availability Statement

All data supporting the findings of this review are derived from previously published studies, reports, and publicly accessible literature sources cited throughout the manuscript.

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