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NEUROPATHOGENESIS OF NIPAH VIRUS INFECTION: MOLECULAR NEUROINVASION, SYNAPTIC DYSFUNCTION, AND NEUROINFLAMMATORY CASCADES

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ABSTRACT

Nipah virus (NiV) is an emerging zoonotic pathogen of the genus Henipavirus that endangers human health with a high fatality rate, neurotropism, and a lack of approved therapeutics. The article is a critical review of the neuropathogenesis of NiV, which dwells on synaptic dysfunction, the integration of molecular neuroinvasion mechanisms, and neuroinflammatory cascades. NiV uses several routes of entry into the central nervous system (CNS), among which are endothelial infection with the breakage of the blood-brain barrier, transportation by leukocytes as a Trojan horse, and direct neuroproliferation through the olfactory tract. In the CNS, the virus is characterized by high neuronal tropism and, at the same time, causes endothelial damage and an immune response, which leads to a dual pathology of vasculopathy and parenchymal encephalitis.

In addition to structural damage, there is emerging evidence that NiV-associated neurological disease is highly influenced by synaptic-level functional pathology comprising neuromodulator imbalance, calcium hyporegulation, and excitotoxicity, all of which impair the integrity of neural circuits. Such mechanisms offer a reasonable account of acute encephalitic expressions, as well as delayed and relapsing neurological syndromes. Although the biology of viruses has been studied, the current treatment methods

are mainly supportive, and the antiviral and immunotherapeutic methods are still being tested. This review shows that there are some critical mechanistic gaps and that synaptic and neuroimmune pathways are currently under-explored but can be used as targets of therapeutic intervention in the future.

Keywords: *Nipah virus, Synaptic dysfunction, Central nervous system infection, Viral immune evasion, Antiviral therapeutics*

INTRODUCTION

The Nipah virus (NiV) is a new and highly pathogenic zoonotic virus that belongs to the genus Henipavirus, being a member of the family Paramyxoviridae, and is characterized by a high rate of case fatality in humans with severe encephalitis and acute respiratory disease (Ganguly et al., 2025). Fruit bats of the genus Pteropus are known to be natural reservoirs of the virus and act as asymptomatic hosts where the virus spills over to intermediate hosts, and humans get infected as a result of contaminated food or direct contact (Paliwal et al., 2024). The rapid progression of the disease that can quickly result in fatal encephalitis or acute respiratory syndrome is a feature of human infection, which contributes to its high virulence (Khan et al., 2024). NiV appears to be a priority pathogen of international health concern due to its ability to propagate from humans to humans, high fatality rates, and absence of effective medical countermeasures; therefore, research on the pathogenesis, transmission patterns, and control methods should be carried out urgently (Tan et al., 2024).

The first outbreak of NiV was documented in 1998-1999 in Kampung Sungai Nipah, Malaysia, which is a piggery, resulting in a large outbreak of the virus in pig farmers. It has epidemic potential, a wide host range, and no approved medications or specific antiviral treatment (Tan et al., 2024; Bruno et al., 2022). After this first outbreak, the outbreaks continued to be reported in South Asia, in Bangladesh, where there have been outbreaks nearly every year since 2001, and in India, including West Bengal and Kerala (Faus-Cotino et al., 2024; Bruno et al., 2022). They have often been linked to consuming raw date palm sap that has been contaminated with infected bat fruit and human-to-human transmission, which further increases the pandemic (Ganguly et al., 2025). One of the notable aspects of the virus is that it is very fatal, and the overall fatality rate of the case is around 40 to 75% (Epstein et al., 2020). The mortality rate was also relatively lower in the Malaysian outbreak (approximately 39-40%) (Sarkar et al., 2025). Conversely, much greater fatality rates have been reported in Bangladesh and India, with some outbreaks (notably) indicating that the NiV infection can be very severe and even deadly.

NiV also has multifaceted neuropathogenic pathways, including vascular and neuronal pathways of central nervous system (CNS) invasion (Quarleri et al., 2022; Goldin et al., 2025). Two main processes are always present. First, the virus causes VI, leading to vasculitis, thrombosis, microinfarction, edema, and hemorrhage in cerebral vessels. Second, it directly infects neurons, resulting in parenchymal encephalitis. Evidence shows neurons are the main targets for viral antigen and RNA (Gazal et al., 2022; Ong et al., 2022). The virus enters the CNS by several routes. These include a blood-brain barrier (BBB) breach by infecting EC, inflammatory cytokines, and a Trojan Horse (TH) mechanism using infected leukocytes (Al-Obaidi et al., 2024). The olfactory pathway is also important; the virus traverses the olfactory epithelium to the bulb and other parts of the brain via the cribriform plate (Bhat et al., 2023). Emerging evidence highlights the choroid plexus and the blood-cerebrospinal fluid (CSF) barrier as possible additional entry sites, underscoring the complexity of NiV neuroinvasion (Marshall et al., 2022).

This review will focus on a detailed study of the neuropathogenesis of NiV infection. More specifically, it will examine the molecular pathways of viral neuroinvasion, the destabilization of synaptic activity, and the role of neuroinflammatory cascades in neuronal injury and disease progression. By combining

experimental and clinical data, the review aims to clarify the main pathogenic mechanisms. It also seeks to highlight possible targets for future treatment interventions.

Virology and Molecular Biology of NiV:

NiV is a negative-sense, non-segmented, non-enveloped RNA virus whose genome is approximately 18.2 kb (single-stranded). This causes it to be one of the biggest viruses of the Paramyxoviridae (Wang et al., 2025). It is a genome with the order of 3 3N-P-M-F-G-G-L 5L 3 and six structural proteins that encode the most important viral processes (Xue et al., 2025). The nucleocapsid (N) protein covers the viral RNA, creating the nucleocapsid. The phosphoprotein (P) is a cofactor of the polymerase. Three accessory proteins (C, V, and W) are generated through RNA editing and alternative reading frames, which help them in immunity evasion (Wang et al., 2025). The protein (M) is the key element of viral assembly and budding. The fusion (F) and glycoprotein (G) play roles in the membrane fusion and host cell receptor attachment, respectively (Moon et al., 2024). The viral genome replication, transcription, capping, and methylation happen to be mediated by the RNA-dependent RNA polymerase (the large L protein). There are also minor changes in the genomic length between the two major lineages: NiV-MY has 18,246 nucleotides, and NiV-BD has 18,252 (Ker et al., 2021).

NiV structural proteins are functionally separated into internal machinery and envelope-associated components that work together to facilitate replication, assembly, and host cell entry (Zhou et al., 2025). These internal machineries are the nucleoprotein (N), phosphoprotein (P), and large polymerase (L). The N protein wraps the viral RNA genome into a helical nucleocapsid, binding the genome in a typical 3-bases-in, 3-bases-out conformation, and stabilizes the structure with interactions between its C-terminal and N-terminal domains (Yang et al., 2024). The P protein is a tetramer that binds the L polymerase to the N-coated RNA and keeps the newly synthesized N protein in an RNA-free (N_0) state to allow appropriate positioning and movement of the polymerase along the genome, its intrinsically disordered regions, and the C-terminal X domain (XD) domain (Peng et al., 2024; Xue et al., 2025). The L protein is a multifunctional enzyme, which comprises RNA-dependent RNA polymerase (RdRp), polyribonucleotidyltransferase (PRNTase), methyltransferase (MTase), and other domains; thus, it facilitates RNA synthesis, 5' capping, and cap methylation (Sutto-Ortiz et al., 2023; Tsukamoto et al., 2024). By contrast, the envelope-related proteins, G, F, and M, are necessary for viral entry and assembly. A tetrameric type II membrane protein, the G glycoprotein attaches to the host cells by binding to ephrin-B2/B3 receptors on the globular head of the protein, which is a six-bladed, 8-spoke, 2-propeller (Wolf & Plemper, 2024). The fusion of the viral envelope with the host cell membrane is mediated by the F glycoprotein, which is a class I fusion protein produced as an inactive form (F^0) and cleaved into F1 and F2 subunits (Salleh et al., 2025). In the meantime, the matrix (M) protein covers the inner side of the viral envelope and is the main component of the coordination of the genome packaging, virion assembly, and budding. The use of a complex mechanism where the viral attachment glycoprotein (G) binds to ephrin-B2 and ephrin-B3 receptors and the fusion protein (F) becomes activated to facilitate the membrane fusion and viral entry of the highly pathogenic species of the Henipavirus genus NiV (Marcink et al., 2023; Yang et al., 2024). The wide distribution of these ephrin receptors in the endothelial and neuronal tissues is what contributed to the high clinical severity of NiV and its universal cellular tropism (Diederich et al., 2023; Satapathy et al., 2025). This virus then replicates its negative-sense RNA genome in the cytoplasm by synthesizing a replication complex consisting of nucleoprotein (N), phosphoprotein (P), and polymerase (L) (Kim et al., 2026). To achieve infection and increase the spread of viruses, NiV employs numerous immune evasion strategies, in particular, the production of the antireceptor of Interferon (INF) by the products of the P gene (V and W proteins) and the inhibition of the antiviral response in the host by the matrix proteins (Bayat et al., 2025). These are all important molecular processes that are important in designing special therapeutic actions against this deadly zoonotic virus.

NiV exploits receptors and a cascade of molecular events to achieve an effective entry of the virus into the host cell, replication, and immunity evasion (Chakraborty et al., 2024). The primary receptor of the viral G glycoprotein is ephrin-B2, which is highly expressed on EC and neurons, which are the most significant targets in NiV pathogenesis, and the secondary receptor is ephrin-B3, which has a lower binding affinity as it dissociates more readily; both receptors include key residues in the G-H loop, which are required during viral attachment (Hoque et al., 2023; Priyadarsinee et al., 2023). The structural studies indicate that the G protein interacts with ephrin-B2/B3 via a conserved interface in which the particular amino acids of the viral and host proteins play a critical role in ensuring that the process of viral and host protein fusion is activated (Nasir et al., 2025; Gurajala et al., 2026). The interaction of receptors with a G protein triggers conformational changes in the G protein to expose the F-triggering stalk domain, which causes the release of the fusion (F) protein to mediate pH-independent membrane fusion at the plasma membrane (Ortega et al., 2022). Interestingly, both monomeric and dimeric forms of ephrin-B2 can trigger allosteric changes in G that will cause complete F activation (Narayanan et al., 2023). Proteolytic cleavage of the F protein per se is required to render this protein fusion competent before it can be incorporated into the budding virions (White et al., 2023).

After infection, the viral ribonucleocapsid complex (N-P-L) causes transcription and replication of the negative-sense RNA genome in cytoplasmic inclusion bodies, and host factors like fibrillarin play a role in efficient RNA production (Sabsay & Te Velthuis, 2023). This is done by the matrix (M) protein and coordinates the viral assembly to include bodies associated with plasma membranes, which is the difference between NiV and other related viruses that use perinuclear sites (Matta, 2025). To be infectious and successful, NiV uses several immune evasion mechanisms, such as IFN signaling by the V protein by blocking the activation and translocation of STAT1/STAT2; inflammatory responses by the W protein; and IFN induction by the M protein, which targets TRIM6 and interferes with IKK6 signaling (Efstathiou et al., 2024). Also, NiV has the capability to hijack host epitranscriptomic responses (including m6A methylation pathways) through the relocalization of METTL3 to increase the stability of viral mRNA and suppress host antiviral responses, allowing effective replication in INF-competent cells.

Mechanisms of Neuroinvasion:

NiV infects the CNS by a complex route of neuroinvasion, both hematogenous and neuronal (Marshall et al., 2022). NiV infects brain ECs with ephrin-B2 and ephrin-B3 receptors in the hematogenous pathway and can directly interact with the BBB and transcellularly enter the brain (Al-Obaidi et al., 2024). This endothelial infection induces a strong inflammatory reaction in the form of cytokine and chemokine release that enhances vascular permeability and tight junction integrity, which undermines the BBB (Zhao et al., 2022). Moreover, extensive vasculitis seen in henipavirus infections is further evidence of the importance of blood-borne viral spreading to the CNS, especially in humans and primate models, although experimental evidence in hamsters indicates BBB disruption may take place after initial CNS infection but not necessarily as the main pathway (Quarleri et al., 2022). Simultaneously, the neuronal pathway is vital, particularly in initial infection. Experimental evidence on hamster models shows that NiV enters the olfactory epithelium first and then moves to the olfactory bulb by olfactory neurons across the cribriform plate, which suggests an early access of the CNS by retrograde axonal transport (Alvites et al., 2023; Wellford & Moseman, 2024). Viral infection then extends to related areas of the brain, like the olfactory tubercle and ventral cortex, and ultrastructural examination demonstrated nucleocapsids in axons (Lebrun et al., 2023). Research in pigs also substantiates a twofold process with cranial nerve and bloodstream dissemination of the CNS. All these results point to the fact that NiV makes use of both hematogenous and neuronal routes, and their proportions differ depending on the host and the stage of infection (Al-Obaidi et al., 2024). The TH mechanism is another technique by which NiV intrusively enters the CNS in the

diseased immune cells (Alghamdi et al., 2025). NiV has been demonstrated to infect immature dendritic cells (iDCs) and monocytic cell lines, including Tohoku Hospital Pediatrics-1 (THP-1), which increases their capacity to move through layers of human brain microvascular ECs, especially when stimulated with TNF-2 (Al-Obaidi et al., 2024). Notably, these NiV-infected leukocytes are capable of maintaining their infectivity after transmigration, which justifies the idea that these leukocytes are carriers capable of introducing the virus to the CNS (Soni & Rameshwari, 2025). Moreover, NiV is able to bind to lymphocytes and monocytes and induce trans-infection of other vulnerable cells, and infected dendritic cells have been shown to cross the BBB in vitro. This entry mode corresponds to the overall concept of TH neuroinvasion, which is a well-established mechanism of neuropathogenic viruses when infected leukocytes serve as vectors to circumvent the BBB and propagate the infection throughout the brain.

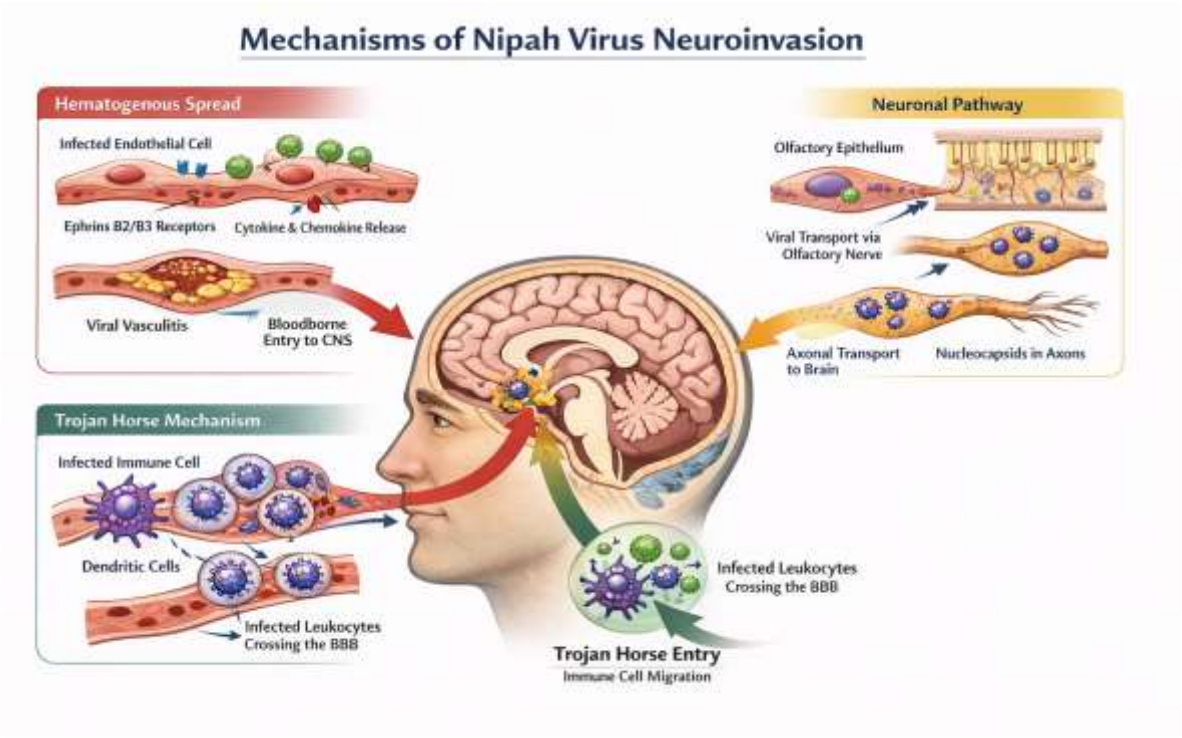

Figure: Major Mechanisms of Nipah Virus Neuroinvasion into the CNS

Diagrammatic representation of NiV neuroinvasion mechanisms into the CNS. The three predominant pathways mentioned in the diagram are (1) hematogenous, through the infection of the endothelial cells and the breakdown of the BBB that results in vasculitis and enhanced vascular permeability; (2) neuronal, through the olfactory epithelium and retrograde translocation of axons to the brain; and (3) the Trojan horse, in which infected These are in the prevalence of CNS infection and neuropathology.

Cellular Tropism and CNS Targeting:

NiV encephalitis is characterized by a combination of vascular injury (VI) and direct infection of CNS cells, as demonstrated by findings from human autopsies, non-human primates, animal models, and ex vivo brain studies (Lv et al., 2025). Neurons are the primary and most extensively infected cell type, particularly in fatal human encephalitis, where abundant viral antigen and RNA are detected in the cerebrum, brainstem, and cerebellum, including within neuronal processes, indicating active interneuronal spread and a central role in disease severity and mortality

(Goldin et al., 2024). In non-human primates, but not humans, glial infection (astrocytes and oligodendrocytes) has been observed, particularly in the brainstem and cerebellum during acute infection, but is relatively spared in humans, compared to neurons (Michaud et al., 2023). Other myeloid cells also play a role in pathogenesis, and NiV continues to persist in microglia along with neurons in surviving primates, whereas the typical form of immune response in acute lesions is the $CD68^{-}$ microglia/macrophages (Michaud et al., 2023). Additionally, brain ECs are key early targets of infection, exhibiting high levels of viral antigen along with pathological features such as vasculitis, thrombosis, and disruption of the BBB (Apoorva & Singh, 2025). The ECs also, develop robust antiviral and inflammatory responses, such as INF-2 and chemokine production, which further enhance vascular injury and neuroinflammation (Duarte et al., 2023). Combined, these results point to the conclusion that NiV encephalitis is caused by a complicated interaction between direct infectioalso developn of neurons and immune cells, as well as by serious vascular pathology.

CNS Cell Types and Roles:

Cell type	Role in NiV CNS disease	Citations
Neurons	Main virus reservoir, major cause of fatalities	(Goldin et al., 2024)
Astrocytes	Infected in some regions; less frequent in humans.	(Chen et al., 2024)
Microglia/CD68+	Dominant inflammatory cell; persistence site	(Ong et al., 2023)
ECs	Entry/transport route; vasculitis, thrombosis	(White et al., 2023)

NiV finds its way into the CNS via multiple complementary routes, bypassing major protective systems (Chen et al., 2024). The BBB is at the heart of things. Brain EC infections result in vasculitis and thrombosis. It also leads to cytokine-mediated increases in vascular permeability, allowing viral entry. NiV glycoproteins are also capable of activating brain ECs (e.g., E-selectin expression) even prior to complete viral replication (Patabendige & Janigro, 2023; Salimi and Klein, 2024). Besides direct invasion by EC, a TH mechanism also aids neuroinvasion. The NiV-infected iDCs and monocytic cells can more readily cross through brain endothelial layers. When they cross the BBB, this movement enables them to infect adjacent cells of the brain (Lawrence and Escudero-Perez, 2022). Neuronal pathways are also necessary along these hematogenous pathways. In hamsters, NiV rapidly enters the brain through olfactory neurons and spreads to the olfactory bulb and ventral cortex by retrograde axonal transport (Chen et al., 2024). CNS distribution in pigs is through cranial nerves and BBB, which facilitates a two-fold entry process. After entering the CNS, the susceptibility of the region appears (Goldin et al., 2024). The brainstem and cerebellum are especially vulnerable to the growth of the viruses and the active infection of neurons and astrocytes in the primates (Maximova et al., 2025). These areas are medically associated with the dysfunction of the brainstem at a severe level and are associated with high mortality. The other important location is the cerebral cortex. Neuronal infection in humans in this instance is more frequent as compared to ischemic lesions in an autopsy. Both neurons and microglia are persistently infected in survivors. Conversely, the white matter shows low levels of

direct infection of glia; its pathology is more associated with microinfarction and vasculopathy. Experimental models also indicate that another vulnerable structure is the choroid plexus, a possible entry point for blood and CSF. However, this structure is not always involved in human autopsy cases (Hosseini & Korte, 2023). Altogether, these data highlight the complicated, multi-path neuroinvasion and region-specific tropism upon which NiV neuropathogenesis relies.

Synaptic Dysfunction and Neural Circuit Disruption:

There is little direct mechanistic data on synapses in NiV infection, but clinical observations and other neurotrophic viral infections provide evidence that there are plausible ways in which synapses and circuits are disrupted in NiV encephalitis (Maximova et al., 2021). Non-NiV primate CNS infections show experimental evidence of lower levels of the protein synaptophysin, a protein of presynaptic vesicles, and structural damage of presynaptic terminals, which is evidence of impaired synaptic integrity (Mohabbat & Baghi, 2025). These structural changes are also accompanied by widespread changes in the gene expression of synapse-related pathways. Such as synapse organization, vesicle cycling, presynaptic calcium regulation, and both glutamatergic and GABAergic transmission systems (Maximova et al., 2021). Neurotropic viral infections are associated with reduced synaptic markers and dendritic spine restructuring in the context of a chronic neuroinflammatory condition, contributing to synaptic dysfunction (Elsharkawy et al., 2026). Also, the invasion of the CNS by the virus may interfere with neurotransmitter signaling by changing genes that mediate neurotransmitter release, calcium-dependent exocytosis, and synaptic vesicle fusion, eventually affecting synaptic transmission. These disruptions can lead to an imbalance in the major neurotransmitters such as dopamine and acetylcholine, hence the neurological impairment as witnessed in NiV-related encephalitis.

Excitotoxicity is one of the major pathways of neuronal damage in NiV encephalitis, with glutamate imbalance and calcium dysregulation being the major factors (Nogueira et al., 2023). It has been known that neurotropic viral infections can increase the level of extracellular glutamate and change the activity of the N-methyl-D-aspartate (NMDA) receptor, which facilitates the excessive influx of calcium, oxidative stress, and eventual neuronal death (Mohabbat & Baghi, 2025). Virus-induced neuroinflammation further contributes to this process, in which the pro-inflammatory cytokines like TNF-α and IL-1β increase the activity of calcium channels and interfere with intracellular calcium homeostasis, leading to synaptic depression and neuronal injury (Sian-Hulsmann & Riederer, 2024). Regularly, gene expression patterns during CNS viral infections indicate a high level of changes in pathways that control cytosolic calcium regulation and calcium-dependent synaptic vesicle exocytosis (Popa et al., 2025). Such molecular and cellular disruptions have more global functional implications at the circuit level, which have clinical implications in survivors in the form of memory, attention, and neurodevelopment deficits in children (Exposito-Alonso & Rico, 2022). Moreover, long-term impairment and dysfunction of synapses and circuits are manifested by common neurological complications, including seizures, encephalopathy, and long-term neuropsychiatric sequelae, with instability of networks caused by impaired excitatory-inhibitory balance.

Neuropathological Findings:

The neuropathology of NiV encephalitis reveals a phenotypical vascular destruction and direct neuronal infection, as seen in human cases through the autopsies and animal models (Ong et al., 2022). A characteristic feature is systemic vasculitis, including endothelial infection, ulceration, fibrinoid necrosis, and thrombosis; and in some cases, multinucleated endothelial syncytia, especially in the CNS, where vasculitis and thrombosis are extremely common (80-90%) and are accompanied by necrotic plaques and encephalomalacia (Cline et al., 2022). The outcome is resultant parenchymal ischemia and microinfarction, which causes discrete lesions of necrotic or vacuolar plaque-like lesions in both gray and white matter; lesions containing viral

antigen and necrosis are commonly related to thrombosis (type 2); and lesions containing necrotic lesions without viral antigen probably result in ischemic or late-stage (Ong et al., 2022; Yang et al., 2024). The major infected parenchymal cells are neurons, which contain a large amount of viral inclusions, antigen, and RNA, which is usually concentrated around necrotic plaques and vasculitic vessels. The pathological characteristics in association are focal neuronophagia, microglial and glial nodules, gitter cell accumulation, and parenchymal loss or encephalomalacia; in chronic or relapsing disease, confluent necrosis, extreme neuronal loss, and vascular proliferation and replacement by reactive gliosis occur. Human pathology is closely similar to experimental primate and hamster models, which have encephalitis with vasculitis, gliosis, rarefaction, spongiosis, and meningitis (Cline et al., 2022). Henipaviruses (including NiV) exhibit a dual pathogenetic process with microinfarction through vasculitis and direct neuronal and glial cell infection in the CNS and other organs. whereas in most other viral encephalitides, vasculitis and systemic thrombotic microangiopathy play a smaller role, and the pathological process is more characterized by direct neuronal and glial cell infection.

Clinical Manifestations of CNS Involvement:

NiV infection is mostly manifested as a high-mortality acute encephalitis syndrome (AES) with rapid progression, often turning into severe involvement of the CNS as a nonspecific one (Chowdhury et al., 2025). The first stage is marked by fever, headache, dizziness, myalgia, and vomiting, and after a few days, neurological symptoms such as impaired levels of consciousness, altered mental status, and significant impairment of the brainstem, such as abnormal doll-eye reflexes, pinpoint or irregular pupils, tachycardia, hypertension, and areflexia or hypotonia, occur (Goldin et al., 2024). Other commonly used features are segmental myoclonus, seizures, focal neurological deficits, and cerebellar signs. AES is the most common clinical manifestation of the disease, which is observed in most outbreaks and, in some cases, with atypical pneumonia or acute respiratory distress syndrome (Sahay et al., 2025). The onset is usually preceded by a brief acute febrile illness that leads to encephalitis, and the clinical course is frequently localized to the brainstem. The acute phase has high rates of case fatality (30-70%), and brainstem involvement has a strong relation to the outcome of fatality; about 15-20% of survivors have long-term neurological impairment (Chowdhury et al., 2025).

Long-term neurological sequelae or delayed complications affect a significant minority of survivors, indicating that NiV infection often causes effects beyond the acute phase (Alzaid et al., 2026). Malaysian studies report that 14-20% of survivors have chronic deficits, including focal weakness, cerebellar dysfunction, movement disorders, depression, cognitive impairment, visual loss, or Horner syndrome (Cline et al., 2022). Survivors may also experience neuropsychiatric effects, such as personality changes and attention or memory deficits. Follow-up MRI usually reveals stable or progressive lesions, but late spinal cord and retinal involvement may also occur. NiV infection is notable for relapses or late-onset encephalitis, occurring months to years after initial illness. In longitudinal studies, relapse developed in 7.5% of patients with prior acute encephalitis (Alam, 2022). Among those without initial symptoms, latency developed in 3.4%, with a mean of 8.4 months and rare cases up to 11 years. Overall, relapse or late-onset encephalitis arises in at least 10% of NiV patients, with fatality rates around 18-20% (Pandeeswari et al., 2023). These episodes present acutely, with fever, headache, seizures, focal impairments, and impaired consciousness. Neuroimaging typically shows patchy or confluent cortical hyperintense lesions, often more widespread than in the original illness. Autopsy and primate studies indicate NiV persistence in neurons and microglia, especially in the brainstem, cortex, and cerebellum, underlies these relapsing events (Satapathy et al., 2025).

Therapeutic Strategies and Targets:

The development of NiV therapeutics is in rapid development, but currently, there are no approved antivirals or vaccines to be used by humans, and most of the evidence is based on an outbreak case

series, animal model, and preclinical trials (Mishra et al., 2024). Ribavirin, one of the antiviral methods, demonstrated a reduction of mortality rate of about 36% in an open-label cohort study in 1998–1999 (Sinclair et al., 2024). Malaysia epidemic, but this effect has not been consistently reproducible in animal models or the subsequent outbreaks, and its overall effectiveness remains questionable (Tang et al., 2024). Small-molecule antivirals like Remdesivir and favipiravir, in contrast, exhibit potent protective activity in animals and are a priority as early treatment or prophylaxis, with remdesivir being the first to undergo clinical trials, either alone or combined with monoclonal antibodies (Pagliano et al., 2022). Other nucleoside reverse transcriptase polymorphs, such as acyclovir and balapiravir, have recorded inconsistent or partial outcomes. Monoclonal antibody therapy against viral glycoproteins is one approach with a particularly promising future; especially, m102.4, the human monoclonal antibody against the G attachment glycoprotein, has shown protection in several animal models and has already been given phase 1 clinical trials, with some of the animal trials as compassionate use. Neutralizing NiV and other henipaviruses and reducing viral escape is achieved by the action of emerging broadly neutralizing antibodies targeting the F and G glycoproteins, including 1F5, 12B2, 5B3, and bispecific constructs such as DS90-m102.4 (Partiot et al., 2024). Recent systematic reviews have shown that m102.4, as a single agent or mixed with remdesivir (and in some studies, 1F5), is best justified to move on to human efficacy trials.

However, despite these achievements, clinical treatment of NiV encephalitis is rather supportive, as it aims at the control of seizures, intracranial pressure, respiratory support, and rehabilitation since no specific neuroprotective or anti-inflammatory agents have been confirmed so far (Krzyzaniak et al., 2023). Although more general neurotropic virus studies point to the possible targets of neuroinflammation, excitotoxicity, and synaptic repair, they are still conceptual concerning NiV (Al-Obaidi et al., 2024). Simultaneously, vaccine development is underway on several different platforms, such as subunit vaccines (e.g., HeV-sG), viral vectors (measles, vesicular stomatitis virus, rabies, and canarypox), virus-like particles, DNA, and mRNA-based (e.g., mRNA-1215) as well as antigen-presenting cell-targeted constructs of NiV (Kozak & Hu, 2023). Several candidates have gone to phase 1 human trials, including HeV-sG-V, PHV02, mRNA-1215, and the monoclonal antibody m102.4, and preclinical data indicate positive effects, including sterilizing immunity with CD40-targeted vaccines in African green monkeys infected with NiV-B. Nevertheless, major issues, such as periodic small-scale outbreaks, make it harder to conduct traditional phase 3 efficacy trials (Oxborough et al., 2025). This has led to efforts to develop alternative regulatory routes, including the U.S. Food and Drug Administration Animal Rule and conditional approval by the European Medicines Agency in terms of immune correlates, as well as the necessity to have standardized immune surrogates and global coordination of vaccine stockpiling and deployment.

Future Direction:

Future studies must also not be based on descriptive pathology but attempt to provide mechanism-oriented and therapeutically amenable information. One of the priorities is the systematic dissection of CNS cell-type-specific responses with the use of such advanced platforms as single-cell multi-omics, spatial transcriptomics, and organoid-based infection models. The methods are able to reveal some hitherto unknown pathways in neuronal vulnerability, viral latency, and immune-mediated damage. The other important direction is the synaptic pathology targeting, which is still a field that is still not that much investigated in NiV research. Exploring the impact of viral infection on proteins of synapses, neurotransmitter dynamics, and circuit-level connectivity may help to discover new biomarkers of disease progression and find new neuroprotective targets. Also, host-directed therapies should be the future research area, such as neuroinflammatory pathway modulation, calcium homeostasis, and excitotoxic signaling. Antiviral agents and monoclonal antibodies can be used in combination with such approaches and could have synergistic advantages and enhance the clinical outcome.

This epidemiological and irregular nature of NiV infections will require new methods of clinical trials and new models of international collaboration to test new treatment therapies and vaccines. While vaccines are being made and approved by the government, researchers should also be looking for reliable immune correlates of protection. Finally, it will be important to combine experimental, computational, and clinical models to make models that can predict how a disease will progress and come back. These interdisciplinary approaches will not only help us gain better knowledge on NiV neuropathogenesis but also enhance the response in the event of future occurrences of this and other high-consequence neurotropic viruses (Afzal et al., 2025; Zahid et al., 2025).

Conclusion:

The neuropathogenesis of NiV infection is driven by the synergistic interaction of vascular, neuronal, and immunological processes, leading to severe CNS damage. Unlike other neurotropic viruses, NiV is the only virus that couples widespread vasculitis and microvascular thrombosis with direct neuronal infection, resulting in a dual-hit paradigm of brain damage. This mixed pathology can not only explain the high mortality rate in acute infection but also account for the presence of viral reservoirs and the occurrence of delayed or recurrent encephalitis.

In this review, it is emphasized that the NiV-induced disease may extend beyond the structural lesions to include profound changes in the way the synapses work and the stability of the neural networks. Excitotoxicity, neuroinflammation, and disturbed neurotransmission interactions become one of the highlights of neuronal dysfunction that are more specific to the development of the disease process and subsequent sequelae. Despite the comprehensive understanding of the entry and immune evasion of viruses with respect to their attempted form, little use of the knowledge of such methods in viable therapeutic regimens has been made. To fill this gap, there is a need to move toward the focus on host-pathogen interactions in the CNS, especially those of neuroinflammation and synaptic integrity. Additional mechanistic understanding will be needed to develop new treatment strategies that can help restrict the amount of acute mortality and the neurological burden in the long term.

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