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THE BRAIN-LUNG-VASCULATURE AXIS: DECIPHERING THE STRAIN-SPECIFIC MECHANISTIC DIVERGENCE OF NIPAH VIRUS PATHOPHYSIOLOGY

Suraj Kumar [1*], Sudarshan Rawani [1], Shivam Kashyap [1], Jiten Gorai [1], Priyangshu Kumar Singh [1], Biplop Debnath [1], Dhananjay Sahu [1], Ronit Tirkey [1], Anish Bara [1], Ajay Kumar [1], Sahitya Chouhan [1], Abhishek Kumar Sinha [1], Karan Kumar [1], Amit Kumar Prajapati [1], Sunty Kumar [1], Naba Kishor Gorai [1], Chandan Pal [1], Nitish Verma [1], Abhishek Verma [1], Rahul Verma [1], Anuranjan Oraon [1], Prakash Kumar [1], Rahul Kumar [1], Akash Kumar [1], Udit Raj [1], Jit Gorain [1], Sumit Shah Gupta [1], Abhijit Kumar [1], Balram Mahto [1], Rajnish Raj [1], Keshav Kumar [1], Shahid Afridi [1], Pinky Kumari [1], Ashmona Lakra [1], Mukti Oraon [1], Neha Kumari [1], Sudhir Kumar Yadav [1], Mintu Prajapati [1], Sujjan Galande [1], Ankit Kumar [1]

[1]Student, Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

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***Corresponding Author: Suraj Kumar**
Student, Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

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ABSTRACT

Nipah virus (NiV), a highly pathogenic henipavirus, causes severe and often fatal disease in humans characterized by encephalitis, acute respiratory distress, and systemic vasculopathy. Two major phylogeographic lineages—NiV-Malaysia (NiV-M) and NiV-Bangladesh (NiV-B)—demonstrate striking differences in transmission dynamics, clinical phenotype, immune response, and tissue tropism. The concept of a "brain–lung–vasculature axis" provides a unifying framework to understand the multi-organ pathogenesis of NiV and the strain-specific divergence in disease outcomes. NiV-M is classically associated with neuroinvasion, endothelial inflammation, and relapsing encephalitis, whereas NiV-B shows enhanced respiratory replication, rapid systemic dissemination, and higher case-fatality rates. Endothelial infection and ephrin-B2/B3 receptor tropism position the vasculature as the central conduit linking pulmonary entry to cerebral pathology. Differences in viral shedding, immune kinetics, cytokine storm intensity, and coagulopathy further shape organ-specific

injury patterns. This review synthesizes current knowledge on molecular virology, host–pathogen interactions, animal models, and clinical observations to decode how strain-level variation remodels the brain–lung–vascular axis. Understanding these mechanistic divergences is essential for developing targeted therapeutics, vaccines, and predictive biomarkers for future outbreaks.

KEYWORDS: Nipah virus, henipavirus, encephalitis, ARDS, endothelial dysfunction, strain variation, vasculitis, neuroinvasion.

1. INTRODUCTION

Nipah virus is a zoonotic paramyxovirus belonging to the genus *Henipavirus* and is recognized as one of the most lethal emerging pathogens affecting humans. Infection produces a spectrum ranging from asymptomatic illness to fatal encephalitis and fulminant respiratory failure. The two major circulating strains—NiV-M and NiV-B—share ~92 % genomic homology yet produce markedly different clinical phenotypes, suggesting that small genetic differences profoundly influence host–pathogen interactions. ***(Lo et al.; Ang et al.)*** Outbreaks in Malaysia (1998–1999) were dominated by neurological disease with limited human-to-human transmission, whereas outbreaks in Bangladesh and India have shown prominent respiratory involvement and efficient person-to-person spread. NiV-B is associated with higher case-fatality rates, shorter disease course, and greater viral shedding from respiratory secretions. ***(Hossain et al.; Clayton et al.)*** The unifying pathological hallmark of NiV infection is widespread endothelial cell infection, which drives vasculitis, thrombosis, and microinfarction across multiple organs. This vascular tropism links pulmonary entry, hematogenous dissemination, and neuroinvasion, forming a functional brain–lung–vasculature axis. ***(Wong et al.; Rockx et al.)***

2. Molecular Virology and Receptor-Mediated Tropism

NiV is an enveloped, negative-sense single-stranded RNA virus encoding structural proteins N, P, M, F, G, and L, along with accessory proteins that modulate immune evasion. Cell entry is mediated by the attachment glycoprotein G binding to ephrin-B2 and ephrin-B3, receptors abundantly expressed on endothelial cells, neurons, and respiratory epithelium. ***(Negrete et al.; Xu et al.)*** This receptor distribution explains the tri-organ tropism central to the brain–lung–vasculature axis. Endothelial infection enables systemic dissemination, while neuronal ephrin expression facilitates direct neuroinvasion and trans-synaptic spread.

(Bonaparte et al.; Mathieu et al.) Strain-specific differences in fusion efficiency, replication kinetics, and interferon antagonism have been proposed as key drivers of divergent pathogenesis. Experimental models demonstrate more rapid pulmonary replication and dysregulated cytokine responses with NiV-B compared to NiV-M. ***(Kasloff et al.; Johnston et al.)***

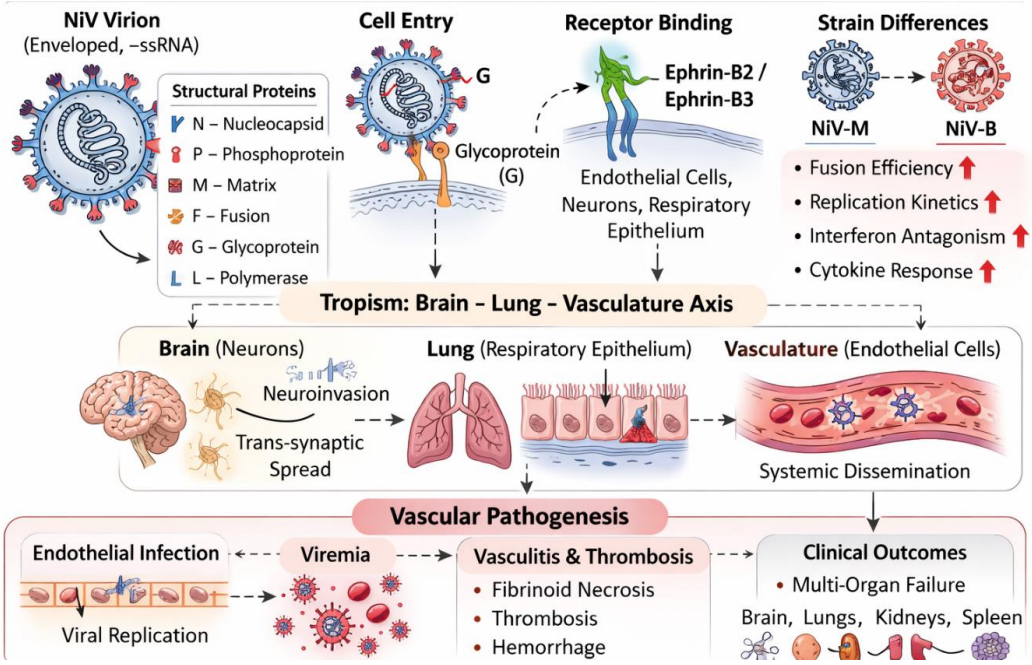

Fig.1. Nipah Virus: Molecular Virology and Receptor Mediated Tropism.

3. The Vasculature as the Central Pathogenic Hub

3.1 Endothelial Infection and Vasculitis

Histopathological studies consistently show systemic vasculitis with endothelial syncytia, fibrinoid necrosis, and perivascular inflammation. Microvascular injury results in thrombosis, hemorrhage, and ischemic infarction in the brain, lungs, kidneys, and spleen***. (Wong et al.; Ng et al.)*** The endothelium acts as both a replication site and a dissemination pathway. Infected endothelial cells release progeny virions into the circulation, facilitating multi-organ seeding and immune activation. ***(Rockx et al.; Escaffre et al.)***

3.2 Coagulopathy and Platelet Dysfunction

Severe disease is frequently accompanied by thrombocytopenia and disseminated intravascular coagulation-like phenomena. These abnormalities reflect endothelial activation, cytokine-mediated tissue factor expression, and platelet consumption***. (Johnston et al.; Mire et al.)*** Notably, NiV-B infection shows more extensive pulmonary vascular injury with fibrin

thrombi and hemorrhage, consistent with a hyperacute vascular collapse phenotype. ***(Johnston et al.)***

4. Pulmonary Axis: Entry Portal and Amplifier of Systemic Disease

4.1 Respiratory Epithelium as Primary Replication Site

Inhalational exposure and oropharyngeal shedding highlight the respiratory tract as a critical early niche. NiV-B produces higher viral loads in respiratory secretions, correlating with efficient human-to-human transmission. ***(Clayton et al.; de Wit et al.)*** Clinical studies report cough, dyspnea, and acute respiratory distress syndrome (ARDS), particularly in Bangladesh and India outbreaks. The higher frequency of respiratory involvement in NiV-B aligns with its enhanced pulmonary replication and endothelial injury**. *(Ang et al.; Hossain et al.)***

4.2 Pulmonary Vascular Injury and ARDS

Diffuse alveolar damage, interstitial pneumonia, and pulmonary hemorrhage are prominent in severe cases. Endothelial disruption increases vascular permeability, leading to non-cardiogenic pulmonary edema and hypoxemia. ***(Rockx et al.; Johnston et al.)*** This pulmonary vascular injury feeds back into systemic disease by amplifying cytokine release and hypoxia-induced inflammation. Thus, the lung acts as both the entry portal and an immunopathological amplifier within the axis. ***(Mire et al.; Escaffre et al.)***

5. Neuroaxis: Mechanisms of Neuroinvasion and Encephalitis

5.1 Hematogenous and Neural Routes

NiV reaches the central nervous system through infected endothelial cells and leukocyte trafficking. Breakdown of the blood–brain barrier allows viral entry into neurons and glial cells. ***(Wong et al.; Mathieu et al.)*** In addition, trans-olfactory and peripheral nerve routes have been proposed in experimental models. These mechanisms explain early neurological symptoms even when viremia is transient. ***(de Wit et al.; Munster et al.)***

5.2 Strain-Specific Neurovirulence

NiV-M is strongly associated with encephalitis, relapsing neurological disease, and long-term sequelae. MRI findings from Malaysian outbreaks show multiple small, disseminated brain lesions corresponding to microinfarcts caused by vasculitis**. *(Wong et al.; Chong et al.)*** Conversely, NiV-B infections often progress rapidly with respiratory failure before extensive neuroinvasion occurs, reflecting a different temporal hierarchy within the axis. ***(Johnston et al.; Ang et al.)***

6. Immunopathogenesis and Cytokine Dynamics

6.1 Innate Immune Evasion

NiV encodes multiple interferon antagonists that suppress early antiviral responses. *Delayed type-I interferon signaling allows uncontrolled viral replication in endothelial and epithelial cells.* ***(Shaw et al.; Park et al.)***

6.2 Cytokine Storm and Immune-Mediated Injury

Fatal cases show elevated levels of IL-6, TNF-α, MCP-1, and other pro-inflammatory mediators. This hypercytokinemia correlates with vascular leakage, coagulopathy, and multi-organ dysfunction. ***(Mire et al.; Johnston et al.)*** Comparative studies indicate a more intense and dysregulated cytokine response in NiV-B infection, which may underlie its higher virulence and rapid clinical deterioration. ***(Johnston et al.)***

6.3 Humoral and Cellular Immunity

Survivors typically mount robust neutralizing antibody responses. Delayed or weak humoral responses are associated with fatal outcomes, particularly in NiV-B infection. ***(Johnston et al.; Guillaume et al.)***

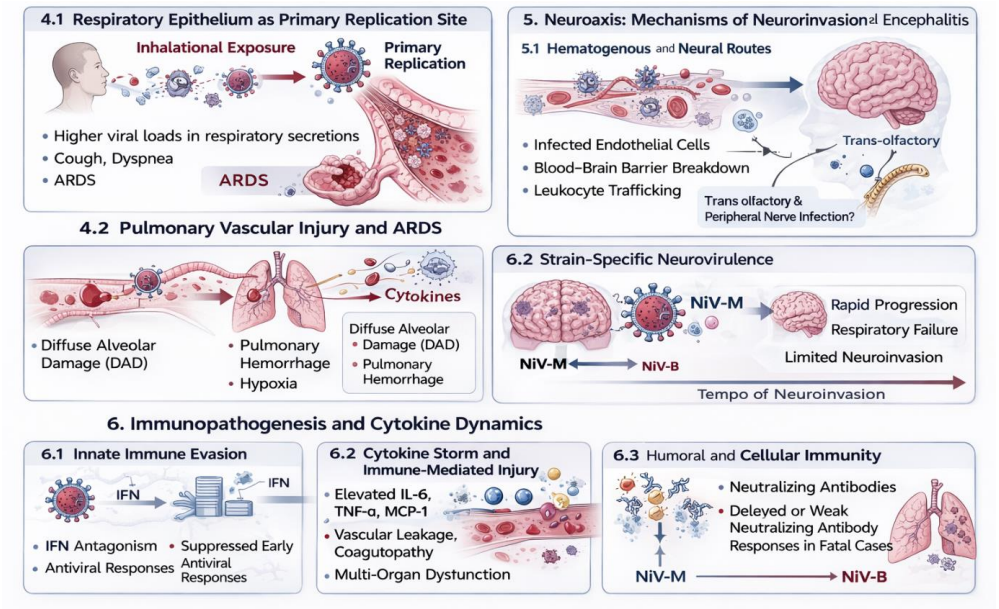

Fig.2. Pulmonary Axis: Entry portal & Amplifier of Systemic Disease.

7. Animal Models Revealing Axis Divergence

Syrian hamsters, ferrets, pigs, and African green monkeys have provided crucial mechanistic insights. Aerosol exposure models show that NiV-M produces heterogeneous disease with prominent neuroinflammation and vasculitis, whereas NiV-B causes rapidly progressive

pulmonary pathology and higher mortality. ***(Johnston et al.; de Wit et al.)*** These findings mirror human clinical patterns and confirm that strain-specific pathogenesis is intrinsic to viral biology rather than solely host or healthcare differences. Early viral clearance and strong antibody responses correlate with survival in NiV-M but are often insufficient in NiV-B infection. ***(Johnston et al.)***

8. Clinical Correlates of the Brain–Lung–Vascular Axis

The temporal sequence of organ involvement differs between strains:

- **NiV-M:** vascular dissemination → cerebral microinfarction → relapsing encephalitis
- **NiV-B:** intense pulmonary replication → systemic vascular collapse → rapid death

Shorter time from symptom onset to death and higher respiratory involvement characterize NiV-B outbreaks. ***(Ang et al.; Hossain et al.)*** Long-term neurological deficits in survivors reflect persistent vascular and neuronal injury. Relapsed encephalitis is thought to result from latent viral persistence in the CNS. ***(Tan et al.; Wong et al.)***

9. Therapeutic and Vaccine Implications

Understanding axis-based pathogenesis enables targeted interventions:

- Endothelial stabilizers to prevent vascular leakage
- Early antivirals to suppress pulmonary amplification
- Immunomodulators to control cytokine storm

Monoclonal antibodies against the G glycoprotein and vector-based vaccines have shown protection in animal models, but strain-specific efficacy must be evaluated**.** ***(Guillaume et al.; Mire et al.)***

10. Future Directions

Key knowledge gaps include:

- Molecular determinants of strain-specific immune evasion
- Mechanisms of viral persistence in the CNS
- Host genetic susceptibility factors
- Biomarkers predicting axis dominance in early disease

Integrating multi-omics, spatial transcriptomics, and advanced imaging will allow real-time mapping of organ cross-talk. ***(Escaffre et al.; Prescott et al.)***

11. CONCLUSION

The brain–lung–vasculature axis provides a comprehensive framework for understanding Nipah virus pathogenesis and its strain-specific divergence. Endothelial infection forms the central pathogenic hub connecting pulmonary entry to cerebral injury. NiV-M and NiV-B differ not only in virulence but in the temporal and spatial hierarchy of organ involvement, immune kinetics, and vascular injury patterns. Decoding these mechanistic differences is essential for precision therapeutics, outbreak preparedness, and risk stratification in future epidemics.

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