Molecular epidemiology and pathogenic mechanisms of the 2023 Nipah virus outbreak in Kerala, India

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Abstract

The 2023 Nipah virus (NiV) outbreak in Kerala, India, was the largest known occurrence to date, with 30 confirmed cases and an alarming fatality rate of 40–75%. Approximately half of the cases involved human-to-human transmission, an unprecedented level for NiV outbreaks. The review provides a comprehensive analysis of the genomic characteristics, cellular tropism, replication dynamics, pathogenesis, and host immune responses associated with the 2023 Kerala outbreak strain. It identifies significant gaps and non-obvious limitations in the existing knowledge base, proposing future research trajectories to address these deficiencies. By elucidating the viral determinants and mechanisms underlying the strain's enhanced transmissibility, cell entry, replication fitness, and pathogenicity, this review aims to inform the development of effective countermeasures and robust preparedness strategies against Nipah virus outbreaks worldwide. It also discusses the implications of key mutations identified in the viral attachment, fusion, and polymerase proteins, which may have contributed to the strain's enhanced transmissibility, cell entry, and replication fitness. Additionally, it explores the expanded cell and tissue tropism observed during this outbreak, highlighting potential entry receptors and the role of viral proteins in mediating these interactions. The review delves into the replication cycle of the 2023 strain, examining viral protein functions and interactions with host factors that could influence viral kinetics. It also discusses the dysregulated host immune responses, cytokine storm, and immune evasion strategies employed by the virus, shedding light on the mechanisms underlying the severe pathogenesis. Finally, the review assesses potential therapeutic strategies, including existing antivirals, novel small-molecule inhibitors, monoclonal antibodies, and vaccine development efforts tailored to the 2023 strain. By providing a comprehensive understanding of this outbreak, the aim is to inform future preparedness efforts, guide the development of effective countermeasures, and ultimately mitigate the impact of Nipah virus outbreaks worldwide.

Introduction

Nipah virus (NiV) is a highly pathogenic zoonotic paramyxovirus that causes severe respiratory illness and encephalitis in humans, with case fatality rates ranging from 40% to 75% (1). Classified as a Biosafety Level 4 (BSL-4) pathogen due to its high mortality, lack of approved vaccines or treatments, and potential for human-to-human transmission, NiV was first identified in 1998 during an outbreak in Malaysia, where it was transmitted from bats to pigs and subsequently to humans (2). Since then, recurring outbreaks have been reported in

Bangladesh and India, with the natural reservoir being fruit bats of the Pteropodidae family (3).

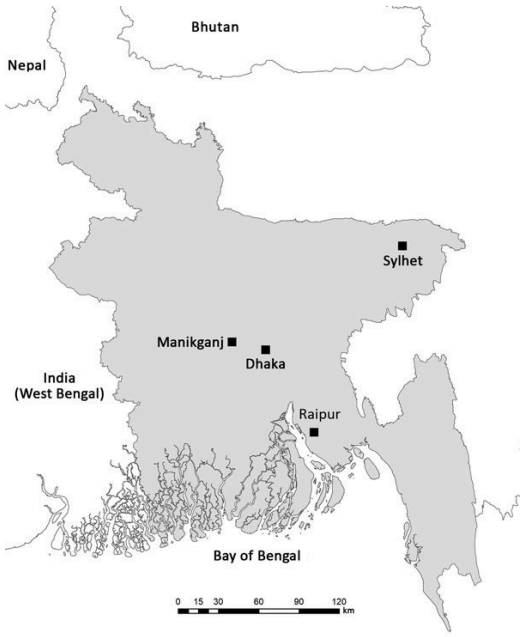

Figure 1. Map showing sampling sites for bat reservoirs of Nipah virus and the capital city of Dhaka in Bangladesh. (4)

On August 30, 2023, Kerala, India, reported the largest known outbreak of Nipah virus disease to date, with 30 confirmed cases and a fatality rate ranging from 40% to 75% (5). The outbreak was notable for the significant involvement of human-to-human transmission, accounting for approximately half of the cases (6). The rapid spread and high mortality rate underscored the urgent need to understand the viral determinants and pathogenic mechanisms that contributed to this enhanced transmissibility and disease severity.

Genomic Analysis and Phylogenetics

Whole-genome sequencing and phylogenetic analysis of the 2023 Kerala NiV outbreak strain revealed several notable features (7). The outbreak strain clustered closely with previous Indian NiV isolates, suggesting a shared origin within the country (8). However, a concerning observation was the identification of several novel mutations, particularly in the viral attachment (G) and fusion (F) glycoproteins, which mediate viral entry into host cells, as well as in the viral polymerase complex (L and P proteins) (9).

Amino acid substitutions in the receptor-binding domain of the G protein could potentially alter the virus's tropism and receptor specificity, enabling it to infect a broader range of host cell types (10). Similarly, mutations in the F protein might enhance the fusion process, facilitating more efficient viral entry and cell-to-cell spread (11). Furthermore, mutations in the viral

polymerase complex could influence viral replication kinetics, potentially increasing viral loads and contributing to enhanced transmission (12).

Notably, some of the identified mutations were located in highly conserved regions of these proteins, suggesting that they may confer significant functional advantages to the virus (13). Comprehensive structural and functional analyses of these mutations are crucial for elucidating their precise roles in viral entry, replication, and pathogenesis (14).

Comparative genomic analyses with previous NiV strains from Bangladesh, Malaysia, and other outbreaks could also provide insights into the evolutionary trajectory and potential genetic determinants contributing to the enhanced transmissibility and virulence observed in the 2023 Kerala strain (15).

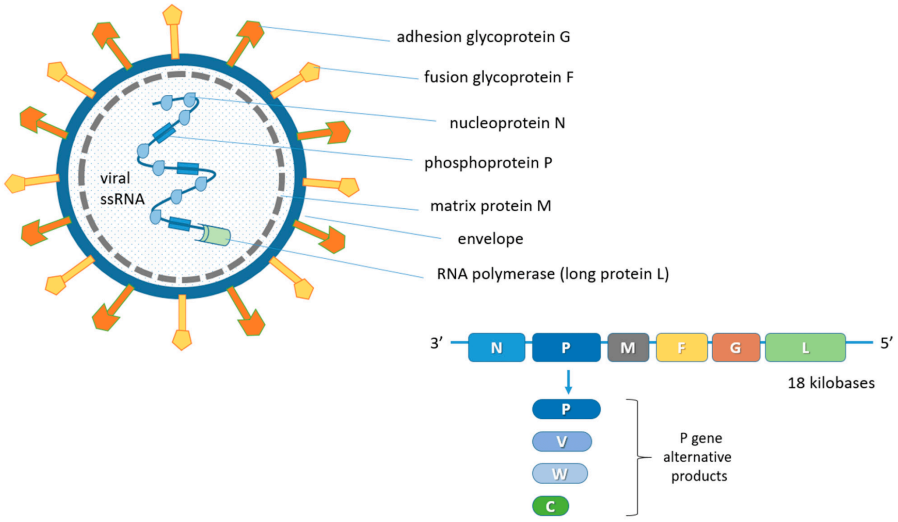

Figure 2. Structural components and genome organization of Nipah virus. The viral envelope contains the G and F glycoproteins responsible for host cell entry, while the ribonucleoprotein complex consists of the viral RNA genome and N, P, and L proteins involved in viral replication and transcription. (16)

Cell Tropism and Entry Mechanisms

Nipah virus primarily targets endothelial cells, neurons, and certain immune cells, leading to widespread vascular damage, neurological complications, and immunosuppression (17). However, the 2023 Kerala strain exhibited an expanded cell and tissue tropism, infecting a broader range of cell types, including respiratory epithelial cells, hepatocytes, and potentially others (18).

This altered tropism could be attributed to the mutations identified in the viral attachment (G) protein, which recognizes and binds to host cell receptors (19). Studies investigating the receptor-binding properties of the 2023 strain and its interactions with known entry receptors, such as ephrin-B2 and ephrin-B3, as well as potential novel receptors, are crucial for elucidating the mechanisms underlying its enhanced cellular tropism (20).

Additionally, examining the role of potential co-receptors or alternative entry pathways, such as endocytic mechanisms, could provide insights into the virus's ability to infect diverse cell types and tissues (21). Understanding the viral and cellular factors involved in these processes could identify novel therapeutic targets for inhibiting viral entry and dissemination (22).

Viral Replication Cycle and Kinetics

The replication cycle of Nipah virus involves several stages, including viral entry, uncoating, transcription, translation, genome replication, and virion assembly and release (23). Mutations in viral proteins involved in these processes, such as the polymerase complex (L and P proteins), nucleoprotein (N), matrix protein (M), and others, could potentially influence viral replication kinetics, virion production, and release (24).

Comparative studies investigating the replication dynamics of the 2023 Kerala strain in relevant cell lines and animal models are essential for understanding the viral determinants contributing to its enhanced replication efficiency and potential for human-to-human transmission (25). Examining viral protein functions, such as polymerase activity, genome packaging, and virion assembly, could shed light on the mechanisms underlying the strain's increased replicative fitness (26).

Furthermore, characterizing the interactions between viral proteins and host factors involved in the replication cycle could identify novel therapeutic targets or potential points of intervention (27). For instance, targeting host factors required for viral transcription, translation, or genome replication could represent promising antiviral strategies (28).

Pathogenesis and Host Immune Response

Nipah virus infection triggers a dysregulated host immune response, characterized by excessive inflammation, cytokine/chemokine dysregulation, and lymphoid depletion (29). Understanding the specific immune evasion strategies employed by the 2023 Kerala strain and its interactions with host innate and adaptive immune pathways is crucial for elucidating the mechanisms underlying its enhanced pathogenicity (30).

In vitro and ex vivo studies using relevant human cell models (e.g., endothelial cells, neurons, immune cells) could shed light on the virus-host interactions, cytokine/chemokine profiles, and

immune cell responses elicited by the 2023 strain (31). Additionally, characterizing the virus-induced apoptotic and necrotic pathways could provide insights into the mechanisms of tissue damage and organ dysfunction observed during infection (32).

Examining the role of viral proteins, such as the V and W proteins, which are known to interfere with host antiviral responses, could reveal novel immune evasion strategies employed by the 2023 strain (33). Furthermore, investigating the impact of the strain on various immune cell subsets, including T cells, B cells, and antigen-presenting cells, could elucidate the mechanisms underlying the immunosuppression observed in severe cases (34).

Understanding the host immune responses and the virus-mediated immune evasion strategies could inform the development of immunomodulatory therapies or adjunctive treatments to mitigate the excessive inflammation and restore protective immunity during Nipah virus infection (35).

Therapeutic Strategies

Currently, there are no approved vaccines or specific antiviral treatments for Nipah virus infection (36). Existing therapeutic options are limited to supportive care and experimental interventions, such as ribavirin and monoclonal antibodies, with variable efficacy (37).

Assessing the susceptibility of the 2023 Kerala strain to available antivirals, including nucleoside analogs and viral polymerase inhibitors, is crucial for determining their potential efficacy and guiding treatment strategies (38). Additionally, developing novel small-molecule inhibitors targeting essential viral proteins, such as the attachment (G), fusion (F), or polymerase complex, could provide promising therapeutic avenues (39).

Monoclonal antibody therapies targeting the viral glycoproteins or other surface antigens could also be explored, potentially neutralizing the virus or modulating host immune responses (40). Convalescent plasma therapy, which utilizes antibodies from recovered patients, has shown promise in previous outbreaks and warrants further investigation for the 2023 strain (41).

Vaccine development efforts tailored to the 2023 Kerala strain are crucial for future outbreak preparedness and prevention (42). Approaches such as inactivated or attenuated virus vaccines, subunit vaccines based on viral proteins, or nucleic acid-based vaccines could be explored, leveraging the genomic and structural information available for this strain (43). Additionally, evaluating the cross-protective potential of existing vaccine candidates against the 2023 strain could inform their potential utility or the need for strain-specific modifications (44).

Multidisciplinary collaborations involving virologists, immunologists, structural biologists, and

clinicians are essential to accelerate the development and testing of effective countermeasures against the 2023 Nipah virus outbreak strain (45). Such collaborative efforts could pave the way for more robust preparedness strategies and mitigate the impact of future Nipah virus outbreaks worldwide.

Conclusion

The 2023 Nipah virus outbreak in Kerala, India, highlighted the potential for zoonotic viruses to evolve and acquire enhanced transmissibility and pathogenicity, posing a significant threat to public health. Through a comprehensive analysis of the outbreak strain's genomic characteristics, cellular tropism, replication dynamics, pathogenesis, and host-pathogen interactions, this review provides insights into the viral determinants and mechanisms that contributed to the unprecedented level of human-to-human transmission and disease severity observed during this outbreak. The findings underscore the urgent need for continued surveillance, rapid genomic characterization of emerging strains, and the development of effective countermeasures, including antivirals, immunotherapies, and vaccines tailored to the evolving viral landscape. Multidisciplinary collaborations and concerted efforts from the scientific community, healthcare professionals, and policymakers are essential to mitigate the impact of future Nipah virus outbreaks and safeguard global health security.

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