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Review Article

Nipah Virus Endemicity In Southern India: A Comprehensive Analysis And Proposed Mitigation Strategies

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ABSTRACT

Nipah virus (NiV), originally identified in Malaysia, has evolved into an endemic concern in Southern India. Over the years, recurrent outbreaks have been observed, particularly in the state of Kerala. This persistence suggests a localized adaptation of NiV-carrying bats, contributing to the region's vulnerability. In response to this ongoing threat, regular screening initiatives and advocating for the safe consumption of products derived from palm trees emerge as critical strategies. By addressing these key factors, there is a potential to mitigate the endemicity of Nipah virus in Southern India, safeguarding public health and enhancing the region's resilience against future outbreaks.

INTRODUCTION

The origin of the term "Nipah" stems from a village in Malaysia, marking the location of the initial outbreak reported in 1998-1999 [1,2]. This outbreak of the Nipah virus (NiV) in Malaysia led to over 250 cases of febrile encephalitis among farmers and butchers, causing widespread panic and significant business disruptions. While Malaysia has not experienced a new epidemic, the Nipah virus has triggered outbreaks in other regions, particularly in Bangladesh and India [2] . The 2018 Nipah virus outbreak in Kerala reignited concerns about the disease, drawing attention to its high mortality rate, diverse disease tropism, multiple transmission routes, including human-to-human transmission, and the impact on healthcare workers' records when epidemics disrupt the medical community. Despite persistent uncertainties surrounding the disease, numerous efforts have been undertaken to unravel its mysteries. This article aims to review and consolidate existing knowledge about the Nipah virus and its clinical manifestations, offering medical information to serve as a valuable guide for healthcare professionals in times of crisis.

THE VIRUS

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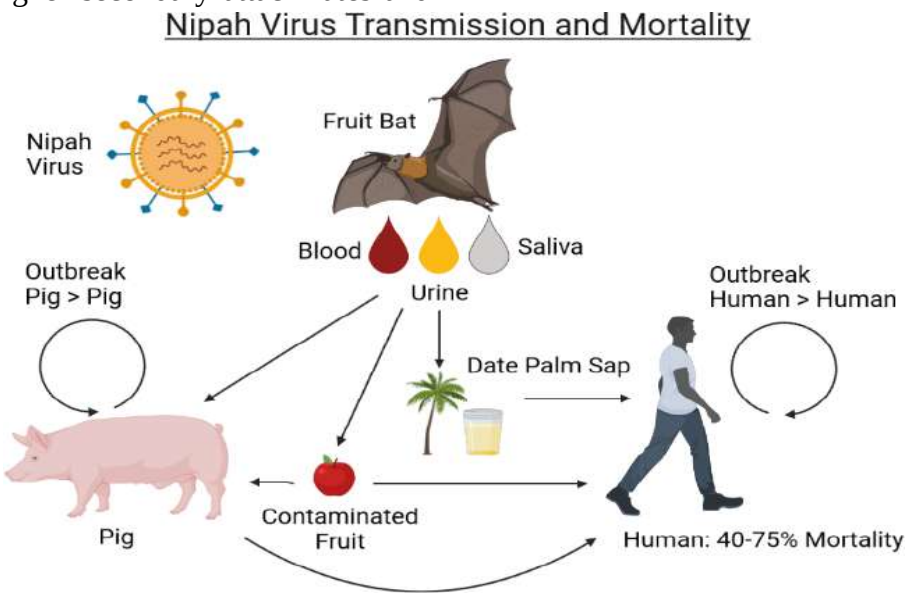
The Nipah virus is characterized as an enveloped paramyxovirus featuring a nonsegmental RNA genome that includes a helical nucleocapsid and exhibits negative polarity. Notably, the Nipah virus displays subtle distinctions in its composition when compared to common paramyxoviruses. In contrast to other members of the paramyxovirus family, it showcases reticular cytoplasmic inclusions in proximity to the endoplasmic reticulum. Moreover, Nipah viruses, on average, have a larger size than typical paramyxoviruses. Minor ultrastructural variations exist between the Hendra virus (HeV) and Nipah virus, both classified as henipaviruses, demonstrating significant cross-reactivity in serological tests [3] . Within the Nipah virus, two distinct lineages have been recognized: the Malaysian (MY) and Bangladeshi (BD) lineages. Upon sequencing, these two strains exhibit an approximate 92% identity. However, a clear distinction arises between pathogenic and infectious aspects. [4-7]

EPIDEMIOLOGY

The initial outbreak of Nipah virus in Malaysia-Singapore (1998-1999) was initially misidentified as Japanese encephalitis (JE) but was later correctly identified as Nipah virus upon further investigation [3,8,9]. The second outbreak occurred in a geographically noncontiguous location, specifically in the Meherpur district of Bangladesh and Siliguri city of West Bengal, India, in 2001 .The Indo-Bangladesh outbreaks differed significantly from the Malaysian outbreak in terms of transmission modes, clinical features, and case fatality rates. In these outbreaks, human-to-human transmission and nosocomial infections (via droplets and/or fomites) played a prominent role. The secondary attack rates were higher, and the disease exhibited more severe and rapidly progressive symptoms compared to the Malaysian outbreak. Besides neurological manifestations, acute respiratory distress syndrome (ARDS) and respiratory failure with multi-organ dysfunction syndrome (MODS) were major contributors to higher mortality. Bangladesh has experienced almost yearly outbreaks, totaling 17 reported until 2015, with a smaller outbreak in the Nadia district of West Bengal, India, in 2007 . The outbreak in the Philippines in March-May 2014 affected both horses and humans, with fruit bats identified as the possible source of infection. Interestingly, this outbreak was significantly associated with horse slaughter and horse meat consumption [10] . The 2018 outbreak in India primarily affected the Kozhikode district and nearby areas of Kerala[11] The Malaysian outbreak was mainly attributed to close contact with affected pigs, with no reported human-to-human transmission [8,12,13] . The Indo-Bangladesh outbreaks, including the recent Kerala outbreak, were distinctive in various aspects, with the mode of transmission being one of them. A significant association was found between NiV disease and the consumption of raw date palm sap contaminated by fruit bats[14] . In a recent development, the Indian state of Kerala has taken preventive measures in response to a re-emergence of the Nipah virus. Schools, offices, and public transport in the Kozhikode district have been closed after two deaths and six confirmed cases. The National Institute of Virology in Pune confirmed that the death of a 49-year-old man on August 30 was caused by the Nipah virus, with a second victim, a 40-year-old man, succumbing on September 11. This marks the fourth occurrence of a Nipah virus outbreak in Kerala since 2018 [15]. The virus remains stable in date palm sap for at least 7 days at 22°C and is tolerant to a wide range of pH (from 3 to 11)[16] . Human-to-human and nosocomial transmission were documented in these outbreaks, with the Siliguri outbreak of 2001 illustrating the transmission of the virus from a single patient to 23 hospital staff and 8 visitors, likely due to poor adherence to standard precautions[17] . Differences in strains (BD vs. MY) contributed to variations in transmission

rates. Ferrets infected with the BD strain showed higher RNA levels in the blood and increased shedding of the virus in oral secretions, potentially explaining the higher secondary attack rates and more severe infection in the Indo-Bangladesh outbreak. Notably, viral shedding was observed even during the incubation period [18] .



CLINICAL SIGNS AND SYMPTOMS

The Highly pathogenic Nipah virus (NiV) induces symptomatic infections in both pigs and humans, with respiratory symptoms being more severe in pigs compared to humans.

In Humans

NiV is responsible for causing severe and rapidly progressing illness in humans, affecting both the respiratory and central nervous systems (CNS) . Symptoms manifest 3–14 days after exposure to NiV, beginning with a notable rise in temperature accompanied by drowsiness and headache. Subsequently, mental confusion and disorientation ensue, progressing to coma within 1–2 days. Encephalitis is a critical complication of NiV infection, with respiratory problems becoming apparent during the initial phase. Atypical pneumonia, coughing, acute respiratory distress, sore throat, vomiting, muscle aches, septicemia, impairment of the renal system, and gastrointestinal bleeding may also occur. In severe cases within 24–48 hours, encephalitis, seizures, and eventual coma may develop . Notably, virus transmission is more common in patients with labored breathing than those without respiratory problems [19-21] .

In Animals

In pigs, NiV induces a disease known as porcine respiratory and encephalitis syndrome (PRES), barking pig syndrome (BPS) in peninsular Malaysia, or a one-mile cough. Pigs under six months of age may experience acute febrile illness with respiratory symptoms ranging from rapid labored breathing to non-productive, harsh coughing. Except for young piglets, mortality is relatively low, but morbidity in confined animals may approach 100%. Neurological symptoms may include muscle twitching, weakness of hind legs, tremors, and varying degrees of flaccid or spastic paresis. Nystagmus and seizures may also occur in boars and sows . In dogs, NiV infection may result in lung inflammation and necrosis of glomeruli and tubules, while cats may exhibit endothelial syncytia and vasculopathy in multiple organs. Experimental NiV infection in various animals, including hamsters, guinea pigs, chick embryos, and African green monkeys, induces lesions in the CNS parenchyma and vasculopathy, although

clinical signs are absent in mice and rats for unknown reasons [22-24] .

Postmortem Finding

Magnetic resonance imaging (MRI) studies in human patients show involvement of the brain's cortex, pons, and temporal lobes, with bilateral abnormalities in the white matter. Disseminated microinfarction in the brain, resulting from thrombosis induced by vasculitis, may occur. Neurons may also be directly involved, with similar vasculitic lesions found in the kidneys, heart, and respiratory tract. Medium and small-sized blood vessels are most affected, leading to syncytia formation and fibrinoid necrosis [25] . Postmortem examinations in pigs may reveal varying degrees of lung consolidation and hemorrhages, froth-filled bronchi, blood-stained fluids in the trachea and bronchi, and congestion with generalized edema in the kidneys and brain. Histological examination may show pneumonia with syncytial cell formation in the endothelial cell lining of blood vessels. Small vessel vasculopathy may develop in the CNS and other major organs, accompanied by generalized vasculitis, fibrinoid necrosis, and mononuclear cell infiltration. Immunohistological examination may reveal viral antigens concentrated in blood vascular endothelial cells, especially in the lungs. In dogs, kidneys may exhibit congestion with severe hemorrhage, and exudates may be present in the bronchi and trachea [23,26] .

DIAGONSIS

Common hematologic abnormalities observed in Nipah virus (NiV) infection include thrombocytopenia (30%) and leukopenia (11%). Elevated liver enzymes are present in 40% of patients, and hyponatremia may also be detected. Hemoglobin, renal indices, and electrolytes other than sodium are typically within normal ranges. Lymphocytic pleocytosis with raised proteins, similar to other viral meningitis cases, may be observed in cerebrospinal fluid . NiV is classified as a biosafety level (BSL) 4 agent; however, routine diagnosis can be conducted in BSL 2 laboratory facilities if the virus is inactivated during specimen collection, and isolation is not attempted. Laboratory diagnosis during the acute and convalescent phases involves a combination of tests. Samples should be transported at 4°C and processed as early as possible. During the early stage of illness, virus isolation and reverse transcriptase polymerase chain reaction assay (RT-PCR) from throat and nasal swabs, cerebrospinal fluid (CSF), urine, and blood are recommended[27] . In the convalescent phase, antibody detection using enzyme-linked immunosorbent assay (ELISA-IgG and IgM) from serum or CSF may be employed. Advanced diffusion-weighted (DW) magnetic resonance imaging (MRI) of the brain can provide useful radiological evidence of Nipah encephalitis[28]. This imaging technique, based on Malaysian experience during the Nipah outbreak, may be particularly valuable in diagnosing Nipah encephalitis and deciding on treatment and post-exposure prophylaxis . MRI studies reveal multifocal discrete lesions in acute Nipah encephalitis, likely due to micro-infarction areas. These lesions, measuring approximately 2-7 mm, are disseminated throughout the brain, mainly in the subcortical and deep white matter of the cerebral hemispheres. No mass effect or edema is typically observed. In relapse or late-onset Nipah encephalitis, MRI characteristically shows multiple areas of patchy and confluent cortical involvement [29,30] .

TREATMENT AND POST – EXPOSURE PROPHYLAXIS

The treatment of NiV disease is primarily supportive, focusing on syndromic management of acute encephalitis syndrome[31] . Specific pharmacological options should not be considered alternatives to infection control measures. Evidence for post-exposure prophylaxis in

individuals with close contact with confirmed Nipah cases is limited, and more research is needed. Three pharmacological options explored for the possible treatment and post-exposure prophylaxis of NiV infection are Ribavirin, m102.4 monoclonal antibody, and Favipiravir.

Ribavirin

In vitro studies and animal studies have shown conflicting results regarding the efficacy of ribavirin against NiV and Hendra. While some studies demonstrated effective inhibition of viral replication in cell lines[32,33] , others in animal models showed that ribavirin treatment only delayed but did not prevent death after Nipah or Hendra virus infection[34,35] . A human study during the Malaysia outbreak of NiV suggested a 36% reduction in mortality with ribavirin treatment. However, as treatment allocation was not randomized, the positive outcomes may be attributed to better general medical care for treated patients. Serious adverse reactions with ribavirin include neutropenia, anemia, lymphocytopenia, and suicidal ideations. The Infectious Diseases Society of America recommended the use of ribavirin in NiV infections in 2008 .

Favipiravir

Favipiravir, a viral RNA-dependent RNA polymerase inhibitor developed as an antiviral for influenza, has shown success in a Syrian hamster model for Nipah virus infection. The results suggest its potential use in NiV treatment [36] .

Monoclonal Antibodies

The most promising monoclonal antibody (mAb) therapeutic for Nipah virus (NiV) infection is currently m102.4. This human cross-reactive antibody has been affinity matured to strongly neutralize both NiV and Hendra virus (HeV) attachment glycoprotein G. It achieves this by blocking the interaction of G with the host cellular entry receptors Ephrin B2 and B3[37] . In preclinical studies on ferrets and non-human primates (NHP), a single intravenous infusion of m102.4 provided full protection against NiV infection in ferrets when administered 10 hours after intranasal infection. Post-exposure studies in African Green Monkeys (AGM) showed full protection even when treatment was initiated up to 3 days post-infection with HeV and 5 days post-infection with NiV-M, even after the onset of clinical symptoms and viremia. A second dose was administered 2 days after the initial one. Notably, the treatment window for NiV-B may be shorter than NiV-M, with m102.4 being protective only when administered up to 3 days post-infection with NiV-B. Compassionate therapy for post-exposure treatment in patients, combined with promising preclinical data, led to a phase I clinical trial. This trial found that m102.4 dosages tested were safe, well-tolerated, and remained active at levels capable of virus neutralization for at least 8 days post-administration. No serious adverse effects leading to participant withdrawal were reported, and no anti-m102.4 antibodies were generated . Another monoclonal antibody under investigation is h5B3.1, a humanized, cross-reactive, neutralizing mAb targeting the fusion glycoprotein F of NiV and HeV. By blocking the conformational change required for membrane fusion and virus infection, h5B3.1 has demonstrated protective efficacy against lethal challenges with either NiV or HeV in ferrets. There is potential for a combination treatment of h5B3.1 and m102.4 antibodies, targeting both viral surface glycoproteins to minimize the chances of escape mutants. However, further in-vivo characterization of h5B3.1 is needed before potential introduction in human patients, alone or in combination with m102.4 .

BATS

Members of the Pteropodidae family, colloquially known as flying foxes or Old World fruit bats, belong to 41 genera and about 170 species. The most species-rich genus is Pteropus, with 59 species, many of which are island endemics.

Pteropodids are strictly vegetarian, foraging for fruits, nectar, and pollen using their sight and a sensitive olfactory system. Some species, like those of the genus Rousettus, use tongue clicks as a crude form of echolocation. Pteropodids play crucial roles in ecosystems as pollinators and seed dispersers. They have a tropical and subtropical distribution in the Old World, ranging from the eastern Mediterranean to South Africa, the Indian Ocean islands, and the northern and western coasts of Australia. Pteropodids typically occur in primary or maturing secondary forests, roosting on large, canopy-emergent trees. Their diet is essential and mostly relies on flowering plants found in woodlands or orchards. Many species are found in coastal areas and drink salt water to supplement nutrients lacking in their diet. Pteropodids are frugivorous and nectarivorous, with some species also consuming flowers. Foraging habits vary, with larger species relying on canopy resources and smaller species using understory resources. Some species have specialized adaptations, like the claws on their thumbs and second digits, to access hidden or inaccessible fruit [38-42] .

KERELA

In the state of Kerala, the coconut palm stands out as the extensively cultivated crop, covering an expansive 7,56,890 hectares in the year 2018–19 . This versatile crop thrives in virtually every corner of the state, taking advantage of Kerala's diverse landforms that include mountains, riverine deltas, wetlands, and varied ecoclimatic conditions ranging from high rainfall zones to rain-shadow regions. The ecoregions in Kerala boast diverse soil types, climates, as well as flora and fauna. The cultivation of principal crops, including coconut, has been deeply ingrained in the agricultural practices of Kerala across these diverse ecoregions since ancient times. While coconut is a major crop in the lowlands, its cultivation has also extended to the midlands and the slopes of the highlands. Along the western seaboard, the shorelines of lagoons and backwaters, and the banks of creeks, the coconut palm is abundantly scattered, creating a distinctive feature in the topography of the state . Noteworthy is the prevalence of coconut palms on the peripheries of the meandering valleys that encompass the numerous hills, further contributing to the unique landscape of Kerala. Despite traditionally being a significant crop in the lowlands and midlands, coconut cultivation has progressively ventured into high-altitude regions, exemplified by the Idukki district. This expansion into high-altitude areas may pose challenges given the potential mismatch with the crop's ecoclimatic requirements[43] . The predominant coconut-producing states in India are the four southern states, namely Kerala, Tamil Nadu, Karnataka, and Andhra Pradesh. These states collectively contribute to over 90 percent of the total coconut cultivation area and production in the country[44]

CONCLUSION

The epidemiological analysis highlights shifts in Nipah virus transmission patterns, clinical features, and severity between Malaysian and Bangladeshi lineages. Kerala's vulnerability stems from abundant palm and coconut trees, bats as virus carriers, and local dietary habits, which are heavily based on palm trees. This unique nexus poses a distinct vulnerability, necessitating comprehensive prevention and management strategies. Promising treatment avenues, such as m102.4, offer hope, while challenges in diagnosis underscore the need for rapid tools. Urgent actions include deepening virus understanding, strengthening surveillance, and enhancing public health infrastructure for swift responses. So by enhanced surveillance of surrounding nature and the bat population monitoring for their patterns , the risk can be lowered tremendously.

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