Penyakit Virus Nipah: Tinjauan Literatur Tentang Kondisi Pengetahuan dan Manajemen Saat Ini

Nipah Virus Disease: A Literature Review of The Current State of the Knowledge and Management

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ABSTRAK *Penyakit virus Nipah adalah infeksi zoonosis dan penyakit baru yang disebabkan oleh virus Nipah (NiV), sebuah virus RNA dari genus Henipavirus, famili Paramyxoviridae, yang ditularkan oleh kelelawar buah jenis tertentu, terutama Pteropus spp. NiV sangat patogenik terhadap berbagai jenis mamalia dan dianggap memiliki potensi pandemi karena penularan dari manusia ke manusia melalui kontak dekat dengan orang yang terinfeksi. Virus ini bertanggung jawab untuk menyebabkan penyakit pernapasan yang parah dan ensefalitis yang mematikan pada manusia dengan gejala yang paling umum adalah perubahan status mental, arefleksia, hipotonia, mioklonus segmental, kelumpuhan tatapan mata, dan kelemahan anggota tubuh. Tidak ada vaksin untuk melawan infeksi NiV pada manusia yang tersedia karena kesulitan dalam menangani virus yang sangat menular dan ganas merupakan salah satu kekhawatiran bersama dengan kesempatan untuk mengumpulkan sampel manusia selama wabah yang terjadi di negara-negara di mana virus NiV menyebar. Protokol isolasi, karantina, dan desinfeksi yang tepat termasuk fasilitas infrastruktur dan personil terlatih dengan pakaian pelindung harus tersedia untuk merespons dengan cepat setelah identifikasi kasus baru.*

ABSTRACT *Nipah viral disease is a zoonotic infection and an emerging disease caused by the Nipah virus (NiV), an RNA virus of the genus Henipavirus, family Paramyxoviridae, which is transmitted by specific types of fruit bats, mainly Pteropus spp. The NiV is highly pathogenic to a broad range of mammals and is considered to have pandemic potential due to its human-to-human transmission through close contact with infected persons. The virus is responsible for causing severe respiratory illness and deadly encephalitis in humans with the most*

common symptoms being altered mental status, areflexia, hypotonia, segmental myoclonus, gaze palsy, and limb weakness. There are no vaccines against NiV infection in humans and are available as the difficulty of dealing with a highly contagious and virulent virus is one of the concerns together with the opportunity of collecting human samples during the outbreaks which occur in the countries where the NiV virus spreads. Proper isolation, quarantine, and disinfection protocol including infrastructure facilities and trained personnel with protective clothing should be in place to respond quickly upon identification of any new case.

INTRODUCTION

Nipah viral disease is a type of zoonotic infection that is caused by the Nipah virus (NiV), an RNA virus that belongs to the genus Henipavirus. This virus is transmitted mainly by specific types of fruit bats, predominantly Pteropus spp. It is an emerging disease that poses a serious threat to global health security and is listed among the WHO's priority list of pathogens that are likely to cause outbreaks needing urgent research and development action. Outbreaks of the Nipah viral disease have been associated with several species of Pteropus bats, such as *P. vampyrus, P. hypomelanus, P. lylei,* and *P. giganteus*, in various countries of South and Southeast Asia, including Bangladesh, Cambodia, East Timor, Indonesia, India, Malaysia, Papua New Guinea, Vietnam, and Thailand (Singh, 2019) (Aditi, 2019). It is believed that the emergence of the virus and the potential for zoonotic transmission to animals and humans are linked to habitat loss for these bats (Thanapongtharm, 2015).

The Nipah virus first appeared in Malaysia in 1998 and has caused multiple outbreaks in South and Southeast Asia. NiV is highly pathogenic to various mammals, and its potential to spread from animals to humans and from person-to-person makes it a pandemic threat. In Bangladesh, drinking raw date palm sap contaminated with excretions from *Pteropus spp*. Fruit bats, also known as "flying foxes," is one of the primary ways of NiV transmission, along with human-to-human transmission through close contact with infected individuals. The transmission pathways vary, including Pteropus-swine-man, human contagion through the consumption of contaminated food, inter-human contagion, and even direct bat-human contagion, which is still a hypothesis. NiV is classified as a Biological Safety Level 4 (BSL 4) pathogen, and access to such laboratories is limited in many countries (Aditi, 2019) (Hassan, 2018).

DISCUSSION

Definition of Nipah Virus

Nipah virus disease is a type of zoonotic disease caused by NiV. The NiV is a paramyxovirus that belongs to the Henipavirus genus, Paramyxovirinae subfamily, Paramyxoviridae family, and the Mononegavirales order. This emerging virus can lead to severe respiratory illness and fatal encephalitis in humans. It is an enveloped RNA virus with helical symmetry, possessing a negative sense, single-stranded, non segmented genome that contains six genes arranged consecutively from 3´-5´. These genes include nucleocapsid (N), phosphoprotein (P), matrix (M), fusion glycoprotein (F), attachment glycoprotein (G), and long polymerase (L). The N, P, and L genes combine with the viral RNA to form the virus ribonucleoprotein (vRNP). The F and G proteins are responsible for attaching the virion to the host cell and facilitating its entry (Figure 1) (Singh, 2019).

The NiV virus can survive for up to three days in some fruit juices or mangoes while it can last for at least seven days in date sap stored at 22 °C. It can resist for approximately 18 hours in the urine of reservoir bats. The virus is relatively stable in the environment, and it remains viable even at a temperature of 70 °C for up to one hour. However, the virus can be completely inactivated by heat at 100 °C for longer than 15 minutes. NiV is easily inactivated by soaps, detergents, and commercially available disinfectants like sodium hypochlorite (Bruno, 2023) (Singh, 2019) (Hassan, 2018).

Epidemiology

In Malaysia between 1998 and 1999, the first cases of human NiV infection were discovered. The virus was named after Sungai Nipah, a small village on the Nipah River. In September 1998, several cases were reported in the Perak state of Malaysia, with symptoms such as fever, headache, and decreased consciousness (Aditi, 2019).

Fruit bats, specifically the flying foxes from the Pteropus genus, as known as megabats, are the natural hosts of NiV. They can spread the virus directly to animals and humans or indirectly through contaminated palm fruits, sap, urine, or feces. Megabats serve as NiV reservoirs in Southeast Asia and sub-Saharan Africa (Bruno, 2023).

NiV is a virus that can infect humans in Malaysia and Bangladesh. In Malaysia, the virus is transmitted to humans through infected pigs, which act as the intermediate host of the virus. The risk of contagion is high due to close contact between humans and pigs and their excrements. In Bangladesh, NiV outbreaks occur during winter, mainly in the central and north-western regions of the country. The NiV reservoir animal in these areas is Pteropus. The virus is transmitted to humans through the consumption of the raw sap of the date palm. This feeding behavior provides scientific knowledge about the route of transmission from bats to humans (Bruno, 2023).

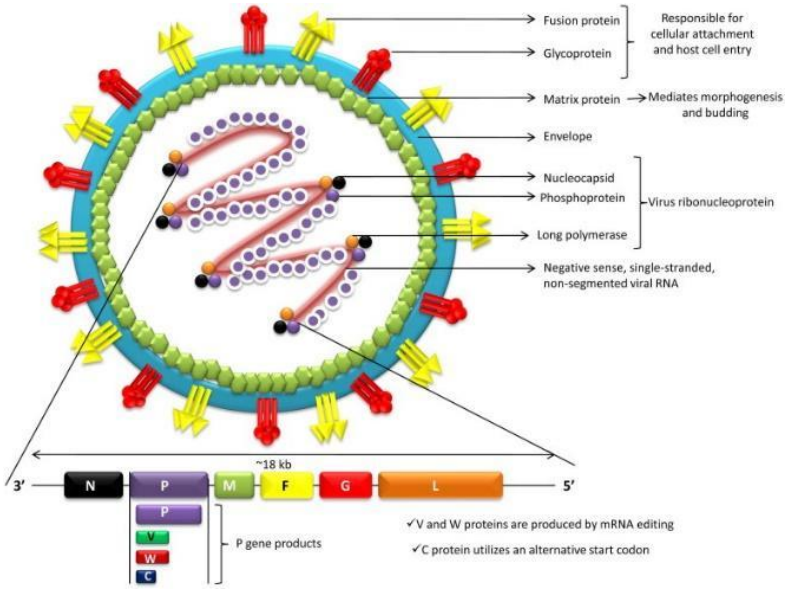

Figure 1. Schematic representation of the NiV structure and viral genome organization (Singh, 2019)

A significantly higher mortality rate of around 70% was observed in India and Bangladesh compared to Malaysia, where only 40% of deaths occurred. Additionally, respiratory disease was prevalent in 70% of Indian and Bengali patients, while there was no significant presence of such clinical signs in Malaysia (Bruno, 2023).

Old age, comorbidities, thrombocytopenia, elevated amino-transferases upon admission, brainstem involvement, and seizures are risk factors associated with a poor prognosis (Aditi, 2019).

Pathogenesis

The virus enters the host's body through the nose or mouth and infects the target cells. As human tissues have only been studied in the advanced stages of the disease, the initial site of replication is unknown. However, high concen-trations of antigen have been found in lymphoid tissue (Waldeyer's ring) and respiratory tissues, indicating that these tissues are likely the sites of initial replication. Once the virus enters the body, it spreads and replicates in the endothelial cells, bronchial epithelial cells, and type II pneumocytes. This fusion is not dependent on pH and is mediated by the absorption of glycoproteins (Bruno, 2023) (Aditi, 2019).

The NiV infection begins by attaching the viral G protein to the ephrin-B2 and -B3 receptors on host cells. Then, within the first week of infection, the virus quickly spreads to various organs like the kidneys, heart, liver, and spleen. These cellular receptors, ephrin-B2 and -B3, are present in various cell types, including epithelial and endothelial cells, and neurons. Moreover, these receptors are highly conserved across animal species, which explains the broad species and tissue tropism of NiV (Liew, 2022).

Viral entry into the central nervous system (CNS) occurs through two distinct pathways: the hematogenous route via the choroid plexus or blood vessels of the cerebrum, and the olfactory nerves. The lympho-hematogenous pathway is the primary route by which the CNS is reached after endothelial damage at the blood-brain barrier. This pathway modifies permeability by releasing inflammatory cytokines such as TNF-α and IL-1β, ultimately leading to the development of neurological signs. Similarly, pulmonary endothelial damage allows the virus to reach the deepest part of the respiratory system. Additionally, there is evidence of direct nerve transmission via the olfactory nerve, as demonstrated in experimental swine models (Bruno, 2023) (Singh, 2019) (Aditi, 2019).

NiV-induced respiratory infection is caused by the production of inflammatory cytokines that recruit other immune system elements, resulting in a condition that resembles acute respiratory distress syndrome (ARDS). This condition is mediated by cytokines such as interleukin (IL)-6, IL-8, IL-1α, monocyte chemoattractant protein 1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). The presence of these mediators in the trachea and bronchi is not always certain, which makes it plausible for respiratory diseases to have low levels of inflammation (Bruno, 2023). Once the virus reaches the respiratory epithelium, it can spread to the endothelial cells of the lungs during the later stages of the disease. Subsequently, the virus can enter the bloodstream and spread freely or via host leukocytebound form, leading to multiple organ failure in target organs such as the lungs, spleen, kidneys, and brain (Singh, 2019). NiV's high lethality can be attributed to its ability to evade the innate immune response (Aditi, 2019).

Clinical Features

The virus is known to cause severe and rapidly progressing illnesses in humans, affecting primarily the respiratory and central nervous systems. Symptoms appear between 3 and 14 days after exposure to NiV, with an incubation period that varies from 4 to 21 days. While some infected individuals may not show any symptoms, most experience a sudden onset of high fever, drowsiness, and headache, followed by mental confusion and disorientation. Within 1-2 days, this may progress to coma, with patients deteriorating rapidly and often dying within days. Additionally, a critical complication of NiV infection is encephalitis, which develops within a week and typically presents with altered mental status, areflexia, hypotonia, segmental myoclonus, gaze palsy, and limb weakness. Some patients may also exhibit coughing, acute respiratory distress, sore throat, vomiting, and muscle aches (Singh, 2019) (Aditi, 2019) (Pillai, 2020).

Diagnose

NiV encephalitis can be diagnosed through the reverse transcriptase polymerase chain reaction (PCR) test, which is the most preferred and sensitive diagnostic test. During the acute phase of infection, cerebrospinal fluid (CSF), blood, nasal/throat swabs, and urine samples can be used for PCR testing for NiV. Patients with NiV encephalitis may present with thrombocytopenia (30%), leukopenia (11%), and deranged liver function tests (40%).

The CSF chemistry in NiV encephalitis resembles that of other non-hemorrhagic viral CNS infections. Haemoglobin, renal indices, and electrolytes other than sodium are typically normal. CSF may show lymphocytic pleocytosis with raised proteins, which is similar to any other viral meningitis (Banerjee, 2019).

Specimens for detecting the virus can be collected from patients showing symptoms or during post-mortem examination. For serological testing, specimens should be collected late in the course of the infection, which is 10-14 days after onset. The National Centre for Disease Control (NCDC) in India recommends collecting throat swabs (in viral transport medium), urine, blood, and/or CSF for diagnosis. It is important to collect samples safely and transport them in triple container packing at a temperature of 2-8°C. Storing samples at -20°C is recommended beyond 48 hours of collection (Aditi, 2019).

Polymerase Chain Reaction (PCR)

PCR is considered to be the most effective method for direct detection of diseases. It is highly sensitive, accurate, and provides rapid results. Specimens such as tissue samples, swabs, CSF, and urine can be used for testing purposes. NiV RNA can be identified by Real-Time PCR (RT-PCR) from respiratory secretions, urine, or CSF. These tests are known for their high degree of accuracy and are commonly used for diagnosing diseases (Aditi, 2019).

Enzyme-linked Immunosorbent Assay (ELISA)

The ELISA test is widely used for serological diagnosis due to its high accuracy, speed, ease of use, and safety. The CDC developed ELISAs for detecting IgG and IgM, which are used to confirm diagnosis. The presence of IgM antibodies in serum or CSF is used to diagnose the disease. Detecting IgG antibodies is a good way to monitor the spread of infection in humans and to identify reservoir animals during epidemiological investigations. It has also been used to diagnose outbreaks in humans (Aditi, 2019).

Differential Diagnosis

It is essential to consider other potential causes of encephalitis in returning travelers. These may include sporadic viral infections, such as Herpes simplex virus (HSV), Varicella zoster virus (VZV), adenovirus, and enteroviruses, as well as epidemic viral infections like Japanese encephalitis virus (JEV), Dengue virus, and Rabies virus.

Additionally, bacterial infections like Rickettsia diseases, tuberculosis, or bacterial abscess, and parasitic infections such as cerebral malaria should also be taken into account (Alam, 2022).

Treatment

During outbreaks of NiV, it is crucial to provide patients with appropriate therapeutics to manage the disease and prevent fatal outcomes. Despite ongoing research efforts, no drug has been approved yet for the specific treatment of this highly important and potentially life-threatening illness (Singh, 2019).

During previous outbreaks of NiV infection, Ribavirin and acyclovir have been utilized as treatment options. In the 1998 Malaysian outbreak, Ribavirin was administered orally or intravenously to patients with NiV encephalitis, resulting in a reduction of the mortality rate by up to 36%. Similarly, during the Singapore outbreak in 1999, acyclovir was given to all NiV encephalitis patients, resulting in only one death being reported due to NiV infection. However, the effective-ness of acyclovir in treating NiV infections remains unclear (Sharma, 2019).

In order to prevent the spread of NiV infection, it is crucial to isolate patients and implement strict infection control measures. Treatment for NiV infection is primarily supportive, focusing on maintaining the patient's airway, breathing, and circulation. It is also important to maintain proper fluid and electrolyte balance. Patients with severe pneumonia and acute respiratory failure may require mechanical ventilation support. In such cases, invasive mechanical ventilation is the preferred method (Aditi, 2019).

Prevention

Effective treatment for the NiV virus is not yet available and there are no widely available vaccines to prevent its spread to humans and animals. Therefore, biosecurity measures play a crucial role in preventing the outbreak of this disease by reducing the risk of transmission (Bruno, 2023).

Efforts to prevent the spread of Nipah virus have primarily focused on three areas: preventing contamination of date palm sap, increasing awareness about the dangers of consuming date palm sap, and preventing person-to-person spread. During an outbreak, the World Health Organization advises that individuals avoid exposure to pigs and bats, as well as consumption of bat-bitten fruits or raw date palm sap/toddy/juice. To reduce the risk of animal-to-human transmission, it is recommended that gloves and other protective clothing (such as masks, protective goggles, gowns, and boots) be worn while handling sick animals or their tissues, and during slaughtering and culling procedures. All protective clothing must be thoroughly washed and disinfected after use.

To prevent person-to-person transmission, infection control practices such as isolation of patients, use of personal protective equipment, and good hand hygiene should be

implemented. Contacts identified through contact tracing should be tested and kept under observation until they test negative. Hospital surfaces have been found to be contaminated by the Nipah virus around patients, highlighting the importance of thorough cleaning and disinfection procedures in healthcare settings (Bruno, 2023) (Aditi, 2019) (Hassan, 2018).

Currently, there are no vaccines available to protect humans against NiV infection due to the complexity of dealing with a highly contagious and virulent virus, as well as the difficulty in collecting human samples during outbreaks in affected countries. However, several strategies have been developed for creating a vaccine against NiV, including subunit vaccines based on the G glycoprotein (sG) of NiV and virus vector-based recombinant vaccines. In animal models, all of these approaches have shown complete protection against oro-nasal NiV challenge after a single dose. The sG vaccine has proven successful in horses, and the VSV vectored Ebola vaccine (rVSV-ZEBOV) has also shown promise. These two vaccine approaches are currently being considered for eventual use in humans (Aditi, 2019).

Prognosis

This specific ailment has a range of case fatality rates between 40% and 100%, indicating its severity. During the outbreak in Malaysia, several factors were identified as having a poor prognosis, including advanced age, severe brain-stem involvement, which often presented as a reduced level of consciousness, vomiting, abnormal doll's-eye reflex, abnormal pupils, hypertension, and tachycardia throughout the progression of the illness. These factors give a clearer picture of the symptoms and outcomes of this particular condition (Banerjee, 2019).

CONCLUSION

NiV is a fatal zoonotic disease that has recently emerged. Bats are the natural reservoirs of the virus and are highly effective in transmitting it to humans, which is why outbreaks continue to occur at regular intervals. Given that bats are found all over the world, it is highly likely that new outbreaks will occur in previously unaffected areas. Unfortunately, there are no approved therapeutic or vaccination options for NiV. Therefore, the best way to control outbreaks is through surveillance and preventive measures. It is particularly important to prioritize the prevention of zoonotic diseases among agricultural and healthcare workers. To quickly respond to any new cases, it is essential to have proper isolation, quarantine, and disinfection protocols in place, including the necessary infrastructure facilities and trained personnel with protective clothing.

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