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Short Communication

Microbiology Section

Nipah: The Jumping Virus

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ABSTRACT

Nipah virus (NiV), infection is an emerging zoonosis with a high mortality rate, and severe neurological and respiratory involvement in humans. NiV, a Paramyxovirus belonging to the genus *Henipavirus* is highly pathogenic and has a mortality rate which varies from 40-100%. It is pleomorphic, spherical to filamentous, ranging in size from 40 to 1,900 nm with a single layer of surface projections. The first epidemic of NiV infection took place in 1998 in Kuala Lumpur, Malaysia whereafter it has spread to Singapore (1999), Bangladesh (2000), West Bengal (Siliguri, 2001 and Nadia, 2007) and Kerala (Kozhikode 2018 and Ernakulam, June 2019) in India. Two lineages of Nipah virus, NiV Malaysia (NiV-MY) and NiV Bangladesh (NiV-BD) have been isolated from humans. Transmission occurs through contact with pigs or related with intake of contaminated date palm sap and human-to-human transmission. *Pteropid giganteus*, the giant fruit bats, are the natural reservoirs and horses and pigs are the amplifying host of NiV. The virus is shed in the urine and saliva of bats, and in the respiratory secretions of horses, pigs and humans. The symptoms are fever, headache and altered level of consciousness. NiV is a pathogen with high virulence. It can be transmitted from animals to humans and then from humans to humans. It not only causes high mortality and morbidity but also spreads panic in the society. NiV has been listed as a category C agent for bioterrorism. There are no effective therapeutic measures to be taken in the event of any outbreak. Hence, timely detection, early diagnosis of cases, preventive measures and supportive care are the mainstays in its management.

Keywords: Chiroptera, *Henipavirus* infections, Saliva, Swine, Zoonosis

INTRODUCTION

The NiV infection is an emerging zoonosis with a high mortality rate, and severe neurological and respiratory involvement in humans. Transmission occurs by ingestion of contaminated date palm sap, contact with pigs and from human to human. Patients present with fever, headache and altered level of consciousness and a high mortality rate. NiV, a paramyxovirus belonging to the genus *Henipavirus* is highly pathogenic and has a mortality rate which varies from 40-100 %. There is no available vaccine against NiV. This article summarises and discusses the epidemiology, clinical and laboratory findings, and treatment during NiV outbreaks across the Asian continent [1].

Epidemiology and Associated Risk Factors

Southeast Asia, since two decades, has been a witness to NiV infection, a paramyxovirus, causing fatal encephalitis. The second member of the genus *Henipavirus* in the family Paramyxoviridae, it is closely related to Hendra virus (HeV). It was exposed during an investigation of the 1994 lethal disease outburst in humans and horses in Australia. In 1998, Malaysia witnessed the first epidemic of NiV, with 258 cases of encephalitis in adults, with a case fatality rate of almost 40%. This was at first thought to be due to Jepanese Encephalitis virus, but fogging for mosquitoes and JE Vaccine did not prevent the spread of the disease. Prof. Sai Lam Kit and his team of microbiologists at the University of Malaya in the Malaysian capital Kuala Lumpur, with the help of Centre for Disease Control, isolated a paramyxovirus which reacted with antibodies to the HeV, but, in viral genome sequencing, was 20% different from HeV. Phylogenetic studies showed that HeV and this new virus were closely linked and distinct from other genera within the *Paramyxoviridae*. The years 2000, 2001, 2007, 2018 and as recently as in June 2019, outbreaks of NiV infections were seen in Bangladesh, Siliguri (West Bengal), Nadia (West Bengal), Kozhikode district in Kerala and Ernakulum district in Kerala respectively. The morbidity and mortality was high among the human population. The mortality in Bangladesh (Meherpur and Naogaon) in 2000 was 70%, much higher as compared to 40% in Malaysia. Respiratory symptoms were common in Bangladesh and West Bengal as opposed to non-specific symptoms of fever, headache, myalgia and sore throat in Bangladesh. In Kerala, it claimed 17 lives in 2018, including a nurse on duty, Line Puthussery, who contracted the infection and died while treating the affected. In 2019, no casualties have been reported till date from Kerala [2-5].

Pteropus giganteus, the Great Indian Fruit Bat is the natural host of NiV. Also, known as the Indian Flying fox, it travels more than 50 km in night, in search of food and water, relying on its sense of vision and smell. They feed on date palm sap (which is collected overnight and is a delicacy in certain cultures), pulp rich food like mango and other fresh food products and help in seed dispersion and pollination, forming an integral part of our ecosystem. However this also constitutes the primary risk factor for NiV transmission. Powered flight of bats allows the efficient spread of viruses and thus the introduction of pathogens to naive colonies. Location of piggeries nearby date palm trees increases the risk of NiV infections, as this virus jumps from bats to the pigs and then onto pig breeders. The risk for transmission in human beings increases with age, being highest in 45 years age and older. Transmission risk is associated with the presence of respiratory symptoms, duration of exposure to infected person and his/her body fluids. A seasonal variation is seen in NiV infection during winter and spring, coinciding with the bat breeding season and date palm harvesting. Unlike Japanese encephalitis and rabies encephalitis, this infection affects more than one person in a household within days or weeks. It needs to be differentiated from herpes simplex, viral encephalitis and leptospiral encephalitis [6-9].

Genome and Phylogenetic Diversity

NiV is a negative-stranded, non-segmented RNA virus. The genome of Malaysia NiV is 18,246 nucleotides (nt) in length, whereas that of the Bangladesh NiV is 18,252 nt. There are six genes encoding the nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion

protein (F), glycoprotein (G), and the polymerase (L). Non-coding intergenic regions separate these six genes. Members of the genus *Henipavirus* have a genome that is distinct from most other paramyxoviruses, in that five of the six viral genes, not including the L gene, contain long Untranslated Regions (UTR) at the 3' end of the viral mRNA transcripts.

Initially this virus was classified as Morbillivirus and named Equine Morbillivirus (EMV) but the analysis of the whole genome showed molecular signatures of HeV not shared by known Morbilli viruses confirming that HeV and NiV are novel Paramyxoviruses. Therefore, in 2002, a new genus, *Henipavirus* was established and approved by the International Committee for Virus Taxonomy (ICTV). There are two strains of NiV, Malaysian (NiV-MY) and Bangladesh (NiV-BD). The outbreak in the Philippines was most likely caused by a NiV-MY strain of *Henipavirus* [3].

Infection and Transmission

A zoonotic infection, the virus circulates in *Pteropus giganteus*, the giant fruit bat, for a brief period of time, during which it gets transmitted to human beings through ingestion of date palm sap or fruits bitten and contaminated by bat urine or saliva. It also gets transmitted to pigs if piggeries are located close to the date palm trees. The acquired ability to infect new host and jump the species barrier is referred to as host-switching, host-jumping or host-shifting. This can lead to infections which might be short and abortive in nature or might trigger an epidemic. A similar epidemiological study from Madagascar revealed host switching of the virus as the dominant evolutionary mechanism [10]. The transmission chain is further carried forward by droplet infection within a meter of very sick patients. In the healthcare facility, risk factors for NiV infection are, close contact, like, touching, feeding, nursing an NiV infected person, thereby exposing to droplet infection [11,12].

The entry of these viruses into host cells is triggered when specific glycoproteins on the viral membrane, the attachment proteins, bind to their appropriate receptors on the host cell membrane. The attachment proteins have separate domains for receptor binding and mediating virus-host membrane fusion [13]. On a molecular level, the host ubiquitin (Ub) system regulates the type 1 interferons which have innate antiviral action. The E3-ubiquitin ligase tripartite motif, also called E3-Ub ligase TRIM6 in short, promotes interferon-mediated innate antiviral immunity. NiV hijacks TRIM6 to promote virus replication. However, the molecular information about how the receptor- binding signal transduces from the receptor-binding domain to the fusion-mediating domain remains unknown [14].

Bioterrorism

High virulence, animal to animal, animal to human and human to human transmission, widespread panic and fear because of its high mortality, inability to control the disease initially, social disruptions, huge economic loss to an important pig-rearing industry (in Malaysia), easy spread from bats to pigs and from pigs to humans and other animals such as dogs, cats, and horses have contributed to it being considered as a potential bioterrorism agent [15].

Clinical Presentation, Signs and Symptoms Along With Long Term Effect on Neurological Function

Nipah infection presents with fever and headache, followed by drowsiness, disorientation and mental confusion and can progress to coma within 24-48 hours. In some, there is respiratory illness during the early part of the infection. The neurological features include signs of altered sensorium, dizziness, vomiting with or without seizures [1]. Presence of brain stem dysfunction or acute respiratory distress both may be present. Persistent convulsions and personality changes are seen as long term effects of NiV on neurological functions. In latent infections, reactivation and death can also be seen months and years after exposure. Approximately, 20% of encephalitis survivors sustain neurological dysfunction including persistent seizures, disabling fatigue, and behavioural abnormalities [13,16,17].

Detection/Diagnosis

Due to the high pathogenicity associated with NiV and HeV, they are classified as Biosafety Level-4 (BSL-4) agents. Safe handling of specimen therefore will require physical infrastructure, personal protection equipment and standard operating procedures [9]. Early diagnosis is critical for suppression of an outbreak and a suggestive laboratory diagnosis and clinical presentation go hand in hand for the detection of NiV infection. A combination of tests is used for laboratory diagnosis of NiV during the acute and convalescent stage.

Early Stages of the Disease

In the early stages of infection, virus isolation or Polymerase Chain Reaction (PCR) is the preferred diagnostic tests. A real time PCR from throat swabs, nasal swabs, blood samples or CSF samples is advised. RT-PCR is the most sensitive diagnostic test available for early detection of NiV [9,12]. Virus isolation is possible only in reference laboratories with BSL-4 facilities. Transportation to designated testing centres should be done adhering to cold-chain procedures (2°C-8°C). PCR is the gold standard test for detection of NiV infection. Currently, most international laboratories are using in-house NiV assays with a variable degree of test validation. A few PCR kits are available commercially, requiring highly trained personnel, larger infrastructure and standardisation. Most reference laboratories are having a variety of RT-PCR, nested PCR, duplex nested and or multiplex PCR which have been developed in-house [4,9,14,18,19].

Later Stage of the Disease/Convalescent Stage

Antibody detection, IgG and IgM by Enzyme Linked Immunosorbent Assay (ELISA), are done during the convalescent stage of the disease. IgM capture ELISA uses the prototype *Hendra* virus antigen and indirect IgG capture ELISA employs the Nipah antigen. PCR is the most sensitive method for diagnosis of active NiV infection, it is considered as a gold standard for NiV detection. NiV-specific IgM ELISA is an alternative approach wherever PCR is not available [9,16]. IgM ELISA is the mainstay of current diagnostic test available for detection of NiV infection. The antibodies reach their peak by 9th day and remain detectable for upto eight months [9]. Being a BSL-4 pathogen, only two institutes in India, Pune's National Institute of Virology and Manipal Laboratory have the testing facilities available for this virus.

Fatal Cases

Immunohistochemistry on tissues collected during autopsy is done in fatal cases for confirmation. Diagnosis in fatal cases through histochemistry is restricted to BSL-4 facilities with stringent safety precautions [9].

Treatment Plan

As there are no drugs currently available to treat NiV infection, symptomatic treatment is done primarily. Management of acute respiratory distress syndrome and encephalitis are the mainstay of the treatment. In severe respiratory and neurologic complications, intensive supportive care is required. At present, there are no antiviral drugs or human vaccines available for NiV [1]. Ribavirin is an antiviral which crosses the blood brain barrier. Use of ribavirin has shown some promise in some initial trials in Malaysia by reducing mortality by 36%. It has also been observed that using ribavirin reduced the extent of ventilator support and the duration of hospital stay to some extent [5]. There are no vaccines available and several vaccine candidates are being assessed in animal models [9,13].

Prevention Strategies

With no vaccines available in the present day, strict infection control measures should be adopted along with barrier precautions. Personal protective equipment such as masks, goggles, gloves, gowns, and boots are mandatory, together with hand washing and disinfection of equipment for those who have to work in the field or on farms where NiV infection is suspected.

In the community, where there is bat population and pig breeding, public outreach programmes should be enhanced to make the people aware about the risks of eating fruits bitten by bats or drinking date palm sap contaminated by fruit bats. Piggeries should be located away from the flora which are a home to the fruit bats. Animal husbandry facilities should be strengthened.

Huge populations of bats contribute to more frequent events of contracting viruses amongst them, as per the "Rule of ecology". The same holds true for human population. Human beings with varied living styles and eating behaviours put themselves at a great risk to many cross-species viral transmission, leading to the threat of emerging viral infections. Jumping viruses, like the bird flu have a historical past and viruses from plants, fish and mammals are equally risky because, cross-species transmission is the most common pattern of their evolution [19].

Relapse or Late Onset of Infection

In the acute phase of NiV infection, the endothelial cells are affected, with syncytial formation, necrosis and systemic vasculitis and brain and respiratory system are affected. However, in late onset of Nipah encephalitis, vasculitis is not seen and infection is limited only to the brain. There is rapid viral replication in the brain parenchyma, after a quiescent period. Patients with acute Nipah encephalitis and non-encephalitic NiV infection during the initial outbreak may later develop relapsed and late-onset Nipah encephalitis after a period of four to eleven years. Transient suppression of immunity or impaired immunity can result in virus reactivation. This can happen due to environmental triggers or infections such as herpes zoster which causes recurrent neuritis [20].

CONCLUSION

Host switching mechanism in NiV, from bats to pigs and from pigs to pig breeders, helps in its' survival and evolution. In this process, human beings become the target of infection which might be a dead end for the virus or may result in an epidemic, depending upon how the infection is tackled. Human beings who consume date palm sap or fruits bitten by bats also risk themselves to infection by NiV, which is secreted in the bat saliva. Knowledge about its host/reservoir, local food cultures, routes of transmission, signs and symptoms, early diagnosis, treatment and late onset complications about NiV, help in the rapid detection and containment of outbreaks, which might be short and abortive in nature or might trigger an epidemic.

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