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Nipahvirus: An emerging threat

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ABSTRACT

Emerging viral infections offer significant threats to humans and animals globally. Nipah viral (NiV) infection is one such potentially fatal- zoonotic disease transmitted between animals and humans. This virus is reported to cause febrile encephalitis and acute respiratory illness in humans with an estimated mortality rate ranging between 40-90 %. NiV has a wide spectrum host range and has resulted in massive livestock loss and economic consequences over the past 24 years since its discovery in 1998.NiV is identified as a priority disease by WHO and numerous researches are being carried out in this area, however, the treatment for NiV in humans is still limited to supportive care. Thus, we are in need of better therapeutic strategies and prophylactic measures to restrict NiV globally. Passive immunotherapy with monoclonal and polyclonal antibodies, nucleotide-derivatives as antivirals, RNA dependent RNA polymerase inhibitors are the recent and promising researches underway.The current review points to the course of NiV infection, transmission and pathogenesis in humans with special focus on the recent therapeutic interventions and prophylactic approaches against NiV.

INTRODUCTION

NiV is an enveloped negative sense single stranded RNA virus of the genus Henipavirus, and family paramyxoviridae. Extensive studies carried out since its discovery have shown that the disease is mostly confined to the geographical areas of southeast Asia, Indian subcontinent and specific regions of Bangladesh; causing seasonal outbreaks during the months of January and March. This further led to the remarkable finding that the virus is transmitted via fruit eating Pteropus bats, which are the indigenous species of these geographical regions. Further substantiating this fact, scientists could also detect NiV specific antibodies from Pteropus bats of the viral affected areas (Luby et al., 2009). The first outbreak of NiV was reported in Malaysia between 1998 and 1999; 105 out of the infected 265 humans died resulting in a mortality rate of 40%. This was a porcine neurological disorder and pigs were the domestic amplifier host, wherein the direct involvement of fruit bats in causing human infection was insignificant (Epstein et al., 2006). The initial viral isolate was made from the cerebrospinal fluid (CSF) of an encephalitic patient native to "Kampung Sungai Nipah", a village in Negeri Sembilan region of Malaysia; and the electron microscopic examination of the virus showed typical features of viruses belonging to the family Paramyxoviridae. And as an afterthought, later the virus was named as Nipah (Nee-Pah). In the later years, similar cases were reported from Singapore as well. In January 2001, around 66 cases of NiV were observed in Siliguri, West Bengal. This was the first ever report from India and had a mortality rate of 68%. Between 2001 and 2005, 5 major outbreaks have been reported from different regions of Bangladesh, all between the months of January and May. During 2014, Mindanao, Philippines, also had confirmed cases of NiV with a mortality rate ranging up to 53 % (Ang et al., 2018). The 2018 Kerala (India) outbreak was devastating with the highest mortality rate of 91%; where human to human transmission was mainly nosocomial in nature, however; fruit eating bats were later identified to be the potential cause. In 2019 and in 2021, remote cases were reported from Kerala.

NiV primarily infects and multiplies in the respiratory epithelial cells, gradually disseminating to the epithelial lining of trachea, larynx and pharynx causing acute respiratory disorders and pneumonia. With increase in the viral load, it targets endothelial cells of different organs, finally spreading the infections all over the infected host organism including the brain and CNS, culminating in encephalitis. Presence of syncytial multinucleated giant endothelial cells in the brain distinguishes NiV from other viral encephalitis. Ranging from mild rhinitis to acute respiratory ailments, neurological disorders or severe vascular damage, the clinical manifestations and course of pathogenesis of NiV elicits greater heterogeneity among patients.

Transmission of NiV

During the initial outbreaks of NiV in Malaysia and Singapore most human infections resulted from direct contact with infected swines or their contaminated tissues. While unprotected exposure to viral containing body secretions or tissue of the sick animal were the primary cause of infection in Malaysia, subsequent outbreaks in Bangladesh and India were due to the consumption of fruits or fruit products (such as raw date palm juice) contaminated with urine or saliva from infected fruit bats. Serological and RT-PCR analysis of blood and urine from pteropid fruit bats from Malaysia outbreak

could detect presence of NiV antigens and RNA substantiating that, bats were the reservoir hosts and pig served as the amplifier host (Chua et al., 2001). Active viruses were detected from the date palm syrup during the outbreaks in Bangladesh as well.

Transmission of NiV from bats to humans may occur in multiple ways; indirectly through domestic animals, eating bat-bitten fruits, consumption of date palm sap contaminated with bat secretions and direct human to human transmission through bodily fluids. Nasal and respiratory secretions play a potential role in human to human transmission of NiV. However, contact with viral contaminated foods and inanimate surfaces can also add to disease incidences. Genetic variability of NiV strain, intense pulmonary involvement, higher rate of viral shedding and human to human spread were the distinctive features of Bangladesh outbreak. Conversely, neurological dysfunctions, thrombotic vasculitis, hemorrhage, and adjacent necrosis culminating in encephalitis were the major clinical characteristics of the Malaysian outbreak.

The 2014 Philippines outbreaks elicited influenza-like symptoms along with neurological dysfunctions in infected persons; and it was interesting to know that neither bats nor swines but horses were the amplifier host. Persons who had contact with infected animals, animal tissues or those who consumed undercooked horse meat were mostly affected (Clayton, 2017). This explains the wide-host range of NiV. Moreover, different studies across the globe have identified viral antigens from the epithelial cells of NiV infected swines, cats, guinea pigs and many other animals. The 2007 outbreak in India was severe and all 5 infected persons died contributing to a100% mortality (Sharma et al., 2019). In the later years many smaller outbreaks were reported from southern parts India; and in majority of the cases Pteropus fruit bats were the reservoir host.

Different strains of NiV have shown different transmission characteristics. Evidence has shown that due to climatic changes and anthropological activities, bats experience stress thus making their immune system weaker, which results in the shedding of viruses. Agricultural expansion, deforestation, human invasion of the sylvatic cycle, urbanization, trade in wildlife, global travel, and other anthropogenic factors have led to increased interaction among humans, domestic animals, and wildlife, increasing the pathogen exchange among these groups.

Owing to this close connection among the environment, humans, livestock, wildlife and their pathogens, a broad ecological perspective is required to understand the reasons for zoonotic disease emergence. There are no reported therapies for NiV infection and thus prophylactic practices are the only possible solution to reduce viral transmission. Culling of infected animals, incineration of carcasses, restricting or banning the movement of animals, wildlife surveillance etc. are the "One Health approaches" under practice.

NiV infection and pathogenesis

Nipah virus (NiV) is a potentially pathogenic and incredibly fatal *paramyxovirus*, accounted to cause respiratory ailments, neurological disorders and severe vascular damage, with case fatality rates ranging up to 100% in affected humans and animals (Baseler et al., 2016). The end stage pathogenesis and clinical manifestations associated with NiV is forever studied with regard to the autopsy samples from the fatal Malaysian outbreak of 1990s, which uncovered the typical pathological features of NiV such as lesions in respiratory system, nervous system, vasculature and to a small extend in lymphatics. Symptomatic infections are usually presented with acute encephalitis and severe pulmonary involvement. While the virus infection with intense pulmonary involvement has a higher rate of viral shedding and human to human spread, fatality associated with the disease is usually due to Brain stem involvement, occurring within 1-2 weeks of symptomatic infection (Baseler et al., 2016; Maisner et al., 2009; Chua et al., 1999). Neurological dysfunctions are primarily due to infection of small blood vessels and the allied thrombotic vasculitis, hemorrhage and adjacent necrosis culminating in the direct infection of specific neuronal clusters. Histopathology as well as detection of viral RNAs through histochemical analyses of tissues procured from fatal human cases, have evidently demonstrated the end stage pathogenesis of NiV infections, in humans and animal models (Lawrence and Escudero-Perez, 2022). However, initial target tissues or how the viruses are transported to the end stage organs remains elusive even now. Extensive experiments using animal models have confirmed that, regardless of the route of administration, the virus invades epithelial cells of upper & lower respiratory tracts, arterial smooth muscle & endothelial cells, neuronal cells and mononuclear lymphocytes, towards the final stage of disease and host termination (Rockx et al., 2011; Torres-Velez et al., 2008).

Viral antigens were identified from the epithelial cells of NiV infected swines, cats and guinea pigs, signifying that epithelium of the oro-nasal and respiratory cavities are the primary site of viral replication. Low level of viremia and presence a viral antigen in CSF has also been reported in these animals (Tanimura et al., 2004; Wong et al., 2002; Mungall et al., 2006). However, viremia has not been demonstrated in any human cases till now. Though there exists no experimental evidence, heamatogenous viral spread across the blood-brain and blood-air barrier might be the major route of NiV to CNS in humans. A 2016 study on NiV infected Syrian hamsters, could detect the viral RNA from nasal turbinates, trachea, larynx and lung within 16 hours post infection. But, the authors failed to detect positive sense viral RNA from cells of the spleen, brain, spinal cord and other organs (Baseler et al., 2016). This is a premiere illustration of the fact that nasal and lung epithelia are the initial target tissue for NiV in the mammalian system. Time dependent tracking of viral antigens and hematoxylin and eosin analysis of infected animal tissues have shown that viruses which are initially replicating in the olfactory and respiratory epithelium, gradually invades the underlying sub-mucosal endothelial cells within a period of 24 hours causing inapparent or placid neutrophilic rhinitis. Though immunohistochemical analyses could detect the viral RNA as well as viral antigens in epithelia, none of the studies have shown the presence of virus in the vascular endothelium in the early stages of the disease (Maisner et al., 2009; Baseler et al., 2016).

Thus, the initial replication and the associated increase in viral load at the primary site would allow the virus to sequentially invade laryngeal and tracheal tissues finally disseminating to bronchiolar epithelium and smooth muscle cells causing pneumonia; this time dependent cascade of disease-pathogenesis have been clearly demonstrated in equines and swines (Kasloff et al., 2019; Khusro et al., 2020). However, involvement of endothelial cells has not been demonstrated in early infection stages. Thus, it is logical to speculate that histological lesions and the wide spread vasculitis which are the typical characteristic features observed in human NiV infections are not the part of "early phase of infection".

Studies on hamsters have proved the presence of viral RNAs and infectious virions in the lymph nodes and spleen at 48 hours post infection. Low levels of viral load were also detected in the brain and spinal cord at these time points. However, none of the studies could demonstrate the presence of either viral RNA, viral antigen or infectious viral particles on any lymphoid organs at any of the early time points (Baseler et al., 2016). This suggests that NiV can strongly bind to human lymphocytes or primate leukocytes facilitating their transfer to other permissive cells like endothelial cells, probably supporting systemic dissemination of viruses. Immunohistochemical analysis or *in situ* hybridization of leukocyte-cell blocks made from terminal heart bleed of infected hamsters could not detect viral RNA (Baseler et al., 2016). In support of this, Mathieu et al., proved that NiV is non permissive to human lymphocytes and monocytes, however, the virus can strongly bind to ephrin receptors on these cells transferring the infections to other permissive cells even without the internalization of virus (Mathieu et al., 2011). Thus, NiV has a remarkable capability to hijack the mononuclear leukocytes and use them as

vehicle to Trans-infect host cells and disseminate the virus all through the host-organism. This would also enable the NiV to infect naïve animals, eliciting a potent and rapid method of viral spread and elevated pathogenicity. Thus in brief, NiV uses the Ephrin-positive leukocytes to 'hitch and ride', initiating an infection in the endothelial cells and disseminating to different parts of the body including CNS (de Boer et al., 2020). This has been proved in vitro by Tiong et al., where they could show the trans-endothelial migration of infectious immature dentritic cells (Tiong et al., 2018). Thus, it is assumed that NiV disseminates from the bordering pulmonary parenchyma to the exterior vascular wall of arteries invading the vascular lumen, entering the bloodstream and spreading the infections through the heamtogenous route; however the exact mechanism adopted for the viral dissemination through vasculature is still unclear.

Pathogenicity and clinical manifestations of NiV infections vary greatly among different species. Clinical signs, pattern of viral shedding, viremia and pathogenicity were distinct among NiV-M or NiV-B inoculated Syrian hamsters, swines, African green monkeys and ferrets (Munster et al., 2012; Baseler et al., 2015). Thus the heterogeneity in pathogenesis across the species and containment restrictions limits the study on NiV infections. NiV is the first BSL-4 agent against which a vaccine was developed; however, the treatment for NiV in humans is still limited to supportive care. Thus the development of novel therapeutic strategies necessitates an in-depth study on the pathogenicity and heterogeneous nature of the clinical manifestations associated NiV.

Defensive antivirals against NiV

Over the past 20 years, NiV has emerged as a potentially pathogenic zoonotic disease causing multiple outbreaks globally. Regardless of its ability to cause severe human infections, NiV can also infect a broad range of mammalian classes including equines and swines. Since its discovery in 1998 NiV has caused barely 700 human cases, however, the involvement of intermediate agricultural hosts and loss of livestock have created massive economic consequences (Johnson et al., 2021). Thus, owing to the alarming spread, disease severity, broad species tropism, zoonotic potential and unattainabilityof better therapeutics, NiV is enlisted in the WHO's Blueprint list of priority pathogens; which explains the need for better therapeutic modalities and countermeasures to control the NiV-pandemic globally.

The broad spectrum nucleoside analogue-ribavirin, is the only clinically utilized therapeutic option for NiV. Ribavirin is one among the "essential medicines" approved by the WHO universally used for the treatment of viral hemorrhagic fevers, Hepatitis C and respiratory syncitial viruses (Banerjee et al., 2019). Ribavirin was initially used in the 1998 Malaysian outbreak, as an open label trial in about 140 patients. The study was reported with 36% reduction in mortality and resulted in fewer neurological defects in disease survivors. The 2018 Kerala (India), outbreak also utilized oral-ribavirin therapy in patients. Two among a subgroup of 6 patients who received oral therapy survived, thereby reducing the percentage of mortality to 20%- in comparison to the control cohort. Furthermore, 8 healthcare workers who were exposed to the clinical infections were given ribavirin as a prophylactic measure and none developed NiV infection (Banerjee et al., 2019; Arunkumar et al., 2019; Chandni et al., 2020). Thoughthe sample size was too small to arrive at statistical significance, the overall ribavirin efficacy was superior but inconclusive during the Kerala outbreak. Nevertheless, the use of ribavirin alone or as a combinatorial treatment along with the antimalarial drug chloroquin was not protective in many animal models (Georges-Courbot et al., 2006; Freiberg et al., 2010). Though a few antiviral drugs have shown potential activity in animal models and human primates, except ribavirin no other therapeutics or antivirals have been utilized for human treatments.

Remdesivir (Veklury®, GS-5734) is a nucleoside derivative which has been reported to elicit 100% survival in aNiV-B challenge in African Green monkey models (Georges-Courbot et al., 2006; Grein et al., 2020). This drug was recently used against Ebola Virus in 2018 Congo outbreak and also as a compassionate therapy against SARS-CoV-2 infections. Even though the efficacy remains unclear, owing to its safety, Remdesivir is still being utilized for multiple enduring clinical trials.Another Drug, Favipiravir (T-705; Avigan®) a purine analogue approved for management of influenza, was found to be 100% effective in small animal models in an NiV-B challenge; none of the animals developed clinical manifestations and no viral antigen or RNA could be detected from their tissues (Dawes et al., 2018). GRFT, a mannose binding lectin, which is under clinical evaluation against HIV, is also a potential candidate in NiV research. This has also shown to have antiviral activity against NiV*in vitro*, and clinical studies are being conducted in hamsters (Mori et al., 2005).4'azidocytidine (R1479), and its derivatives (2'F-4'N3-C and 2'diF-4'N3-C) and another drug ALS-8112 have also shown to have higher therapeutic index and efficacy *in vitro*againsthenipaviruses (Klumpp et al., 2006).They were found to be less cytotoxic and highly effective in controlling NiV infection in lymphoblastoid cells (Lo et al., 2020).

Targeting replicative machinery of viruses, inhibiting viral fusion with host membrane, Viral RNA degraders, *in silico*designed defective interfering particles and epigenomic studies are the promising antiviral researches for NiV underway.

Impending monoclonal antibodies and vaccines against NiV under research.

While the safety and efficacy associated with the majority of the antivirals are inconclusive, passive immunotherapy with monoclonal or polyclonal antibodies designed specifically against viral glycoproteins has been proved as a successful strategy in limiting NiV infections. Several monoclonal antibody (mAb) based studies carried out in hamster models were found to be 100% effective in controlling the clinical manifestations and transmission of NiV infections (Guillaume et al., 2006). However, the "m102.4" is the only reported human mAb candidate awaiting an imminent approval to be used against Hendra and Nipah viruses in humans (Zhu et al., 2008). This ephrin specific mAb has been proved to be exceptionally potent in neutralizing both NiV and Hendra Viruses. The post exposure efficacy of m102.4 has been demonstrated inanumber of animal models including non-human primates (Bossart et al., 2009; 2011). In 2010, owing to a high risk condition, WHO had approved a special request from Australian health authorities to use m102.4 in two individuals exposed to Hendra virus; and eventually the individuals did not develop the disease. Even though m102.4, is used as compassionate therapy in high risk groups the clinical trials in humans are still under way. One of the other antibody therapies under consideration is a humanized, cross-reactive mAb specific to NiV Fusion protein F- "h5B3.1". This mAb is reported to avert viral fusion with the host membrane and is found to be 100% effective as post infection therapy in ferrets when given intraperitoneally (Broder et al., 2013). However, the in vivo characterization of h5B3.1 is still inadequate, and might require additional proof of concept studies to be used in humans.

Immunization strategies using vaccines is the promising "on-health –solution" against NiV. A 2014 study using recombinant vaccinia virus was found to be extremely effective and protective against NiV. Soluble-oligomeric form glycoptrotein subunit vaccine (HeV-sG) has also been massively evaluated against NiV(Bossart et al., 2005). Owing to the remarkably high HeV-sG vaccine-mediated protection observed during oronasal challenge in equines, this vaccine was recommended to be used as protective strategy in equines from 2012 in Australia. "Thus, EquivacHeV® evolved as the first and the only licensed vaccine-commercially deployed against a BSL-4 agent".

A 2022 study, published in PNAS, suggests that aNiV glycoprotein expressing Vesicular somatitis viral vector (Rvsv-rVSV-ΔG-NiVBG) could completely protect monkeys from NiV infection.

The study was pertinent not only in developing an effective immunization strategy but also in opening up a new avenue in demonstrating the effectiveness of using r-VSV based vaccines for rapidly protecting humans against NiV (Foster et al., 2022).There are multiple vaccines under investigation against NiV, and most studies have tried to assess the protection after a 4-5 weeks of infection, however, immediate control of the outbreaks require rapidly acting prophylactic measures.

It was on July 11th 2022 the most astounding statement in the field of Nipah viral research came from NIH, that National Institute of Allergy and Infectious diseases (NIAID-NIH) is launching an early stage clinical trial of a Morderna (in collaboration with MIT and Cambridge) developed experimental vaccine against NiV. The vaccine utilizes an mRNA-platform technology and the dose escalation responses will be evaluated in the study. A retrospective cohort study started in 50 Nipah survivors in Bangladesh in March 2022, is also a promising project;such breakthrough researches not only augments the scientific knowledge about the virus, but the biological materials collected from survivors would also facilitate development of novel research tools and assays.

Use of soluble ephrin-B2 extracellular domains, inhibitors against viral enzymatic machinery, epigenetic or epi-transcriptomic studies, viral mimicking particles are the promising researches "on the go' against henipaviruses. Despite these hopeful results and the continued threat elicited by NiV, no vaccine candidate has progressed towards market for either animals or humans. Thus, extensive research in this area is obligatory for the development of better therapeutics: besides facilitating the control of NiV, such studies would also assist to restrain other haemorrhagic viruses as well.

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