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Review Article

NIPAH VIRUS: A REVIEW

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ABSTRACT

Nipah virus, recentaly recognized, highly pathogenic, a previously unknown paramyxovirus was the main cause of the encephalitis outbreak in Malaysia. This virus can cause severe encephalitis and respiratory problem. Despite of this severe pathogenicity at present there are no approved vaccines or passive immunization therapy available for preventing or treating nipah virus infection in humans or animals. Nipah virus shares many similar characteristics to Hendra virus. Because of their homology, a new genus called Henipavirus (Hendra + Nipah) was introduced. Nipah virus infection fatality rate ranges from 40-70%, sometimes as high as 100% in some outbreaks. In Malaysia 265 cases were observed during 1998 to 1999. In Bangladesh during period 2001–2007, 7 outbreaks of Nipah virus infection were identified. This review covers many of the aspects of the outbreak caused by this new nipah virus, with main emphasis on the structure of virus and its effects on human health. This review also covers recent development in the treatment for deadly nipah virus which include some antiviral agents like Rabinavir and Fabinavir and human monoclonal antibodies mAb, m101, m102.4.

KEY WORDS: *Nipah virus, Hedra virus, Paramyxovirus.*

INTRODUCTION

Nipah Virus Infection (NiV) is an emerging infectious disease of public health importance in the South-East Asia Region [1]. Between September 1998 to May 1999, Malaysia and Singapore were hit by an outbreak of fatal encephalitis caused by a novel virus from the paramyxovirus family [2].

The encephalitis was initially thought to be Japanese encephalitis, but later was shown to be due to Nipah virus, a previously unknown paramyxovirus [3]. This virus was subsequently named as Nipah virus, after the Sungei Nipah village in Negeri Sembilan, where the virus was first isolated [2]. Nipah virus is recently recognized, zoonotic paramyxoyvirus that causes severe disease and high fatality rates in people [4]. This virus along with Hendra virus comprises a new genus designated Henipavirus in the subfamily Paramyxovirinae. The paramaxyvirusses are the group of negative sense single stranded RNA virus [5].

History:

The first human cases of disease attributed to Nipah virus occurred in late September 1998 in the northern city of Ipoh. The cases were first attributed to the Japanese encephalitis (JE) virus; however, the epidemiology of the disease was not consistent with JE. Most of the cases were in adult males who had direct contact with pigs. In March 1999, Malaysian researchers identified the virus as a previously unknown paramyxovirus. The virus was first called Hendra-like virus because it is similar to the Hendra virus, first identified in horses in Australia in 1994. The virus is now named after the village near Kuala Lumpur from where it was first isolated [6].

In 2001, NiV was again identified as the causative agent in an outbreak of human disease occurring in Bangladesh. Genetic sequencing confirmed this virus as Nipah virus, but a strain different from the one identified in 1999. In the same year, another outbreak was identified retrospectively in Siliguri, India with reports of person-to-person transmission in hospital settings. Unlike the Malaysian NiV outbreak, outbreaks occur almost annually in Bangladesh and have been reported several times in India [7]. In the period between 1998-2008 has infected 477 people were infected and killed 252 [39].

In 2014, the Philippines National Epidemiology Center received a report of human deaths in villages on Mindanao, an island in the Philippines. An outbreak investigation revealed additional human deaths and nonfatal infections with concurrent neurologic disease and sudden deaths in several 115 horses [8].

Recent in 2018, NiV was again identified as the causative agent in an outbreak of human disease occurring in Kerala. More than 10 people died.

Aetiology of Virus:

The NiV is classified under the subfamily Paramyxovirinae in the family Paramyxoviridae that comprises the five genera Respiro-, Morbilli-, Rubula-, Avula-,and Henipavirus [9]. This virus is non-segmented, negative stranded RNA genome consisting of helical nucleocapsides encases in an envelope forming pleomorphic virus particle G [5]. The genus Henipavirus contains two of the most pathogenic viruses known in humans, Hendra- and NiV, which were discovered only in 1994 and 1998, respectively [10, 11]. The genome consists of six genes namely nucleoprotein (N), phosphoprotein(P), matrix(M), fusion(F), glycoprotein(G) and large RNA polymerase(L) [12]. The genome of Henipa group of viruses is large (around 18250 nucleotides) as compared to other members of paramyxoviruses due to an extended open reading frame of the P gene and to longer non-coding regions for all the genes except L gene [13]. The F protein of both HeV and NiV are 546 amino acid type I transmembrane proteins that form

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trimers on the cell surface and are responsible for mediating the fusion of virus and host cell membranes during infection [14]. The NiV and HeV matrix (M) proteins have length of 352 amino acids and like other paramyxovirus M proteins are very basic, with isoelectric points of 9.99 and 9.44 respectively [15]. The ribonucleoprotein (RNP) complex of paramyxoviruses consists of an N protein encapsidated genome and viral RNA dependent RNA polymerase complex formed by the L and P proteins [16, 18]. The N proteins of henipaviruses are 532 amino acid proteins responsible for encapsidating the viral genome [16]. The L protein of paramyxoviruses is the largest and the least abundant viral protein found in an infected cell. The large size of the protein reflects the many different enzymatic functions attributed to it, including initiation, elongation and termination of both mRNA transcriptions [16]. The henipavirus P protein is a 707 (HeV)/709 (NiV) amino acid protein, and is the only essential gene product encoded by the P gene for genome replication[16].The P gene of henipaviruses encodes at least three nonstructural proteins (C, V, and W) in addition to the P protein [17]. The P gene of Henipaviruses encodes at least three nonstructural proteins (C, V, and W) in addition to the P protein [18] however, P protein is the only essential gene product for genome replication. The additional gene products are usually not required for virus replication in vitro, though they often serve as virulence factors in vivo [19, 20].

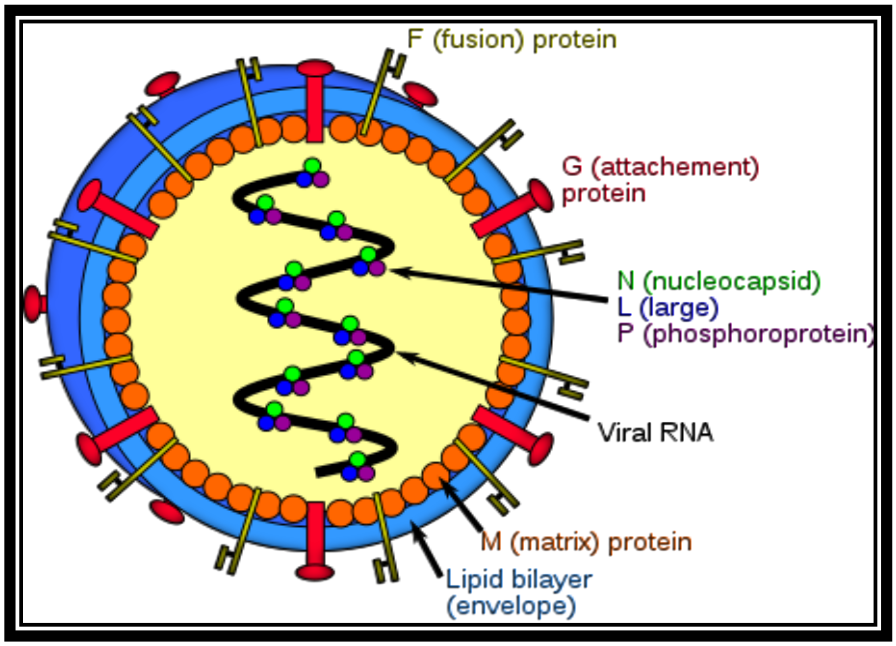

Fig. 1: Structure of Henipavirus

Reservoir of Virus:

Fruit bats of the genus Pteropus have been identified as natural reservoirs of NiV. A seroepidemiologic study in Malaysia implicated four fruit bat species, Pteropus hypomelanus, P. vampyrus, Cynopterus brachyotis, Eonycteris spelaea, and an insectivorous bat, Scotophilus kuhlii [21]. However, Hendra and Nipah viruses possess an exceptionally broad species tropism and both natural and experimental infections have demonstrated their capacity to cause disease which can often be fatal in horses, pigs, cats, dogs, ferrets, hamsters, guinea pigs, monkeys, and humans, spanning 6 mammalian Orders [22].

The Mode of Transmission:

Infected bats shed virus in their excretion and secretion such as saliva, urine, semen and excreta but they are symptomless carriers. The NiV is highly contagious among pigs. The direct contact with pigs or fresh pig products was responsible for NiV transmission to humans [23]. Direct contact with infected pigs was identified as the predominant mode of transmission in humans when it was first recognized in a large outbreak in Malaysia in 1999 [24].

There is strong evidence that emergence of bat-related viral infection communicable to humans and animals have been attributed to the loss of natural habitats of bats. As the flying fox habitat is destroyed by human activity the bats get stressed and hungry, their immune system gets weaker, their virus load goes up and a lot of virus spills out in their urine and saliva [25].

Introduction of NiV infection into the human population occurs by two mechanisms of spillover from flying foxes: transmission via an intermediate animal host, which precipitated the outbreak in Malaysia; and bat-to-human transmission, which has occurred in Bangladesh and India. Transmissions via an intermediate animal host as well as food-borne transmission of a putative NiV were observed in the Philippines [4].

Symptoms:

Infection with Nipah virus is associated with encephalitis (inflammation of the brain). After exposure and an incubation period of 5 to 14 days, illness presents with 3-14 days of fever and headache, followed by drowsiness, disorientation and mental confusion. These signs and symptoms can progress to coma within 24-48 hours. Some patients have a respiratory illness during the early part of their infections, and half of the patients showing severe neurological signs showed also pulmonary signs. During the Nipah virus disease outbreak in 1998-99, 265 patients were infected with the virus. About 40% of those patients who entered hospitals with serious nervous disease died from the illness. Long-term sequelae following Nipah virus infection have been noted, including persistent convulsions and personality changes. Latent infections with subsequent reactivation of Nipah virus and death have also been reported months and even years after exposure [26].

Dignosis:

Laboratory diagnosis of a patient with a clinical history of NiV can be made during the acute and convalescent phases of the disease by using a combination of tests. Virus isolation attempts and real time polymerase chain reaction (RT-PCR) from throat and nasal swabs, cerebrospinal fluid, urine, and blood should be performed in the early stages of disease. Antibody detection by ELISA (IgG and IgM) can be used later on. In fatal cases, immunohistochemistry on tissues collected during autopsy may be the only way to confirm a diagnosis [27].

Viral antigen capture ELISAs would also provide a high throughput format at relatively low cost for screening of the samples. The development of monoclonal antibody based antigen capture ELISAs for virus detection and for differentiation between NiV and HeV [27].

Polyclonal antibody derived from the immunization of rabbits with NiV-G protein DNA vaccine construct was used for development for a novel antigen-capture sandwich ELISA system. It is suggested that

considering the recent emergence of genetic variants of Henipaviruses and the resultant problems that arise for PCR-based detection, this system could serve as an alternative rapid diagnostic and detection assay [28].

Treatment and Future Aspect:

Despite the pathogenicity of henipaviruses, no approved vaccines or therapeutics are available for use in humans [29]. Treatment of human patients with HeV or NiV infection remains dependent on supportive care. Ribavirin, a broad-spectrum anti-viral agent, was used in NiV infected patients during the outbreak in Malaysia [30]. Ribavirin is a well-known first line treatment for suspected viral infections of unknown etiology. Ribavirin exhibits antiviral activity against a wide variety of both RNA and some DNA viruses [31] and is an approved treatment for several viral infections [32]. In vitro studies have shown that ribavirin is effective against both Hendra and Nipah virus replication [33]. Ribavarin may alleviate the symptoms of nausea, vomiting, and convulsions. Treatment is mostly focused on managing fever and the neurological symptoms. Severely ill individuals need to be hospitalized and may require the use of a ventilator [34]. Also anti-malarial drug chloroquine was shown earlier to block the critical proteolytic processing needed for the maturation and function of the Hendra virus F glycoprotein [35] and not surprisingly cholorquine was later shown to inhibit Nipah and Hendra virus infection in cell culture [36]. The first successful treatment of henipavirus infection *in vivo* with a small molecule drug is favipiravir. Favipiravir has demonstrated efficacy against a broad spectrum of RNA viruses, including members of the *Paramyxoviridae*, *Filoviridae*, *Arenaviridae families*, and the *Bunyavirales* order. Favipiravir (T-705) is a purine analogue antiviral approved for use in Japan against emerging influenza strains; and several phase 2 and 3 clinical trials are ongoing in the United States and Europe [29].

The development of humanized monoclonal antibodies and their successful use in treatment of Hendra and Nipah virus infections in animal models has shown promising acceleration in the treatment of Nipah virus. The first fully human monoclonal antibodies against Hedra and Nipah viruses, which can cause high mortality (upto 75%) were recently developed, one of them m101 shown exceptional potency against infectious virus [37, 38].

CONCLUSION

Nipah virus is very dangerous infectious agent. At present, there are no approved vaccines or passive immunization therapy available for preventing or treating henipavirus infection in humans or animals. But since from few years tremendous efforts has been taken to develop effective therapeutic agent against nipah virus. At the outbreak of Malasiya Rabinavir an antiviral agent has been used for the treatment of nipah virus. Fabinavir antiviral agent is also undergoing clinical trials in US and Europe. At present recently developed mAb, m101 m102.4 has shown exceptional potency against infectious virus.

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