

Nipah Virus New Emerging Zoonotic Disease by

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Abstract

Nipah virus, a paramyxovirus related to Hendra virus, first emerged in Malaysia in 1998. It is an emerging zoonosis with the potential to cause significant morbidity and mortality in humans and major economic and public health impacts. Bats are the main reservoir for this virus, which can cause disease in humans and animals. There are currently no effective therapeutics, and supportive care and prevention are the mainstays of management.

Introduction

More than 60% of the newly identified infectious agents that have affected people over the past few decades have been caused by pathogens originating from animals or animal products. Nipah Virus (NiV) represents a new emerging zoonosis, one of the most important bat-borne pathogens discovered in recent era [1].

The first outbreak in Malaysia resulted in the eventual killing of about 1.1 million pigs. It was categorized as zoonotic biosafety level 4 (BSL4) agent, depending upon the geographic distribution of outbreaks, it is responsible of case mortality between 40% to 100% in both humans and animals, thus one of the most fatal virus known to infect humans [2].

Aetiology:

Nipah is an enveloped, negative-sense, single-stranded RNA virus, with a genome size of about 18,000 nucleotides. NiV genome organization comprises six major genes present in all *Paramyxovirus*: RNA polymerase and nucleocapsid genes (N, P and L); envelope membrane protein genes (F and G); and matrix protein (M). The attachment (G) glycoprotein which binds the viral receptor, and the fusion (F)

glycoprotein which causes virus-host cell membrane fusion, are the two membrane-attached envelope glycoproteins responsible for host cell infection by NiV [3].

As other animal *Paramyxovirus*, the virus is inactivated by 60°C for 60 minutes. It is stable between pH 4.0 and 10.0. It survives for long periods in favourable conditions, for days in fruit bat urine and contaminated fruit juice. It is susceptible to common soaps and disinfectants. Lipid solvents, such as alcohol and ether, and sodium hypochlorite solutions were used in outbreaks for disinfection [4].

Natural Host

Fruit bats (*Macrochiroptera*) of the family *Pteropodidae*—particularly species belonging to the *Pteropus* genus—are the natural hosts for Nipah virus. There is no apparent disease in fruit bats. Bats belonging to the genus *Pteropus* are widely distributed. They live in the tropics and subtropics of Asia, including the Indian subcontinent, Australia, Indonesia, Madagascar, and a number of remote oceanic islands in both the Indian and Pacific Oceans [1].

Transmission

During the initial outbreaks in Malaysia and Singapore, most human infections resulted from contact with sick pigs or their contaminated tissues. Transmission is thought to have occurred via droplets, contact with throat or nasal secretions from the pigs, or contact with the tissue of sick animals [5]. During the later outbreaks in Bangladesh and India, Nipah virus spread directly from human-to-human through close contact with people's secretions and excretions. In Siliguri, India, transmission of the virus was also reported within a health-care setting, where 75% of cases occurred among hospital staff or visitors [5].

CLINICAL PRESENTATION

Humans

The incubation period ranged from 4 days to 2 months, with more than 90% at 2 weeks or less, the symptoms are characterized by high fever followed by seizure and death due to encephalitis or respiratory disease. Human infections range from asymptomatic infection to fatal encephalitis. Infected people initially develop influenza-like symptoms of high fever, headache, muscle pain, sore throat and weakness. This can be followed by impairment in spatial perception and stability, feeling sleepy, altered consciousness, and neurological signs, sometimes accompanied

by nausea and vomiting that indicate acute encephalitis [1]. Some patients infected with NiV Bangladesh strain can also have atypical pneumonia and severe respiratory problems, including acute respiratory distress [6].

Encephalitis and seizures occur in severe cases, progressing to coma within 24 to 48 hours. The case fatality rate estimates 40- 100% during sporadic outbreaks. Most people who survive acute encephalitis make a complete recovery, but around 20% are left with residual neurological consequences such as persistent convulsions and personality changes. A limited number of recovered patients may experience encephalitic relapse up to years later and subclinically infected individuals may show central nervous signs up to 4 years later. The brain was the most severely affected organ .Other affected organs were the kidney, lung, and heart [1].

Diagnosis

Nipah virus infection can be diagnosed by a number of different tests. Since Nipah is classified as a biosafety level 4 (BSL4) agent, special precautions must be undertaken in the collection, submission and processing of samples. Biosafety considerations require that this work be carried out only in a physical containment level 4 (PC4) facilities. Various strategies have been developed to reduce the risk of laboratory sera, including gamma-irradiation or sera dilution and heat-inactivation. Henipa virus antigens derived from tissue culture for use in ELISA can be irradiated with 6 kilo Greys prior to use, with negligible effect on antigen titre [7].

Identification of the agent

virus isolation by cell culture can be performed from brain, lung, kidney and spleen samples transported at 4°C in 48 hours or frozen if over 48 hours, using African green monkey kidney (Vero) and rabbit kidney (RK-13) cells. Cytopathic effect (CPE) usually develops within 3 days. Monolayers are examined for the presence of syncytia after incubation for 24–48 hours at 37°C. Henipavirus-induced syncytia are characterised by presence of large multinucleated cells containing viral antigen. In absence of CPE, two 5-day additional passages are recommended to confirm negative results. Immunostaining or virus neutralization tests (plaque reduction, microtitre

neutralization, immune plaque assay) are applied to characterize the virus isolate and differentiate cross reactivity within henipaviruses [1].

Polymerase Chain Reaction (PCR) assay and real-time PCR can be applied with the advantage of not propagating live infectious virus. Immunohistochemistry can be applied on formalin-fixed tissues or formalin-fixed cells of vascular endothelium from brain, lung, mediastinal lymph nodes, spleen, kidney, uterus, placenta and foetus, using antisera to NiV, rabbit antisera to plaque-purified NiV or biotin-streptavidin peroxidase-linked detection system [7].

Serological tests

Serum Neutralisation (SN) test is designated as the reference standard for anti-henipavirus antibody detection [7].

Cultures are read at 3 days, and those sera that completely block development of CPE are designated as positive. Immune plaque assay is an option in case of cytotoxicity. Indirect or capture enzyme-linked immunosorbent assay (ELISA) can be applied on for detection of IgG and IgM, respectively. Due to false-positives related to specificity of ELISA, positive reactions have to be confirmed by SN [8].

Treatment:

There are currently no antiviral drugs or vaccines available to treat Nipah virus infection for either people or animals. Intensive supportive care with treatment of symptoms is the main approach to control the infection in people and consisted of anticonvulsants, treatment of secondary infection, mechanical ventilation, and rehabilitation [9].

With nothing known at the outset of the outbreak in Malaysia, empirical treatment was started with ribavirin, chosen for its broad-spectrum activity against DNA and RNA viruses and ability to cross the blood-brain barrier [10].

Experimentally, the therapeutic use of a neutralizing human monoclonal antibody, the m102.4, which recognizes the receptor binding domain of the NiV G glycoproteins, appeared promising in a ferret animal model. Furthermore, the m102.4 was also successfully tested in Non Human Primate (NHP) models against challenge with related Hendra virus [11].

PREVENTION

As treatment options are limited, focus on NiV management should be on prevention.

To date, prevention of Nipah virus infection relies on veterinary measures in domestic animals and public health education. Preventive strategies include interventions to prevent farm animals from acquiring NiV by eating fruit contaminated by bats. Farms should be designed to reduce overcrowding to avoid rapid spread of disease between animals and should not be near fruit trees that attract bats. Consumption of contaminated sap should be avoided. However, efforts to reduce fresh sap consumption in general would be unpopular, as they go against social and cultural norms. Other, more acceptable methods would include physical barriers to prevent bats from accessing and contaminating sap [12].

A number of vaccine candidates have been found to be capable of complete protection against NiV disease in preclinical studies of small animal and nonhuman primate models. Candidate vaccines using a vesicular stomatitis virus vector are the most advanced, having demonstrated protection in hamsters, ferrets, and African green monkeys [13]. Fortunately, a new international coalition of governments and pharmaceutical companies called the Coalition for Epidemic Preparedness Innovations (CEPI) was formed in January 2017 to develop safe, effective, and affordable vaccines for diseases with pandemic potential, such as NiV[14].

CONCLUSION

NiV emerged as a new virus exactly 20 years ago, causing severe morbidity and mortality in both humans and animals. As the reservoir host *Pteropus* is widespread, and NiV has been found in bats in various countries, the potential for outbreaks to occur in new regions remains significant.

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الملخص العربي

فيروس نيباه ، وهو فيروس مرتبط بفيروس هيندرا ، ظهر لأول مرة في ماليزيا في عام ١٩٩٨ . وهو مرض حيواني ناشئ يصاحبه احتمالية تسبب معدلات كبيرة من المرض والوفيات في البشر والتأثيرات الاقتصادية والصحية العامة. الخفافيش هي المستودع الرئيسي لهذا الفيروس ، والذي يمكن أن يسبب المرض عند البشر والحيوانات. لا يوجد حاليا أي علاج فعال ، والرعاية الداعمة والوقاية هي الوسائل الأساسية لمواجهته.

