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Nipah Virus Encephalitis : A New Emergent Zoonotic Disease
โรคไข้สมองอักเสบนิปาห์ : โรคสัตว์สู่คนตัวใหม่

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มีการระบาดของโรคไข้สมองอักเสบในมาเลเซียและสิงคโปร์ระหว่างเดือนกันยายน 2541 ถึงเดือนมิถุนายน 2542 ผู้ป่วยเป็นคนงานในฟาร์มเลี้ยงสุกรในมาเลเซีย และคนงานในโรงฆ่าสัตว์ในสิงคโปร์ ที่มีประวัติสัมผัสกับสุกรที่ติดเชื้อโดยตรง ระยะแรกของการระบาดเข้าใจว่าผู้ป่วยติดเชื้อไข้สมองอักเสบเจอี (Japanese Encephalitis) แต่ต่อมามีการพิสูจน์พบไวรัสชนิดใหม่ที่เป็นสาเหตุนี้ว่าอยู่ในกลุ่มพารามิกโซไวรัส ชื่อ นิปาห์ (Nipah virus) การระบาดเกิดขึ้นครั้งแรกที่เมืองคินตา รัฐเปรัก มาเลเซีย แต่แยกเชื้อไวรัสครั้งแรกจากผู้ป่วยในหมู่บ้านนิปาห์ รัฐเนเกริเซมบิลัน มียอดผู้ป่วยรวมทั้งสิ้นในมาเลเซียกว่า 265 ราย เสียชีวิต 105 ราย ในสิงคโปร์มีผู้ป่วย 11 ราย เสียชีวิต 1 ราย ผู้ป่วยส่วนใหญ่มีอาการปวดศีรษะ วิงเวียน มีไข้ อาเจียน และหมดสติ อาการทางระบบประสาทที่เด่นจำเพาะได้แก่ กล้ามเนื้อกระตุกเป็นส่วน ๆ กล้ามเนื้ออ่อนแรงและไม่ตอบสนองต่อการกระตุ้น ความดันโลหิตสูง และหัวใจเต้นถี่ ผลการตรวจน้ำไขสันหลังและเลือด พบว่าติดเชื้อไวรัสนิปาห์ ผู้ป่วยที่เสียชีวิตอาจเนื่องจากมีพยาธิสภาพที่ส่วนก้านสมองอย่างรุนแรง การติดต่อและแพร่กระจายของโรคยังไม่ทราบแน่ชัด พาหะของเชื้ออาจเป็นค้างคาวกินผลไม้ (fruit bats) ซึ่งไม่แสดงอาการ แต่ตรวจพบเชื้อไวรัสในปัสสาวะ ขณะนี้ยังไม่มียาหรือการรักษาจำเพาะต่อการติดเชื้อไวรัสชนิดนี้ การควบคุมและป้องกันโรคทำโดยการกำจัดสุกรที่ติดเชื้อ และคอยตรวจหาเชื้อไวรัสอย่างสม่ำเสมอ ในประเทศไทยยังไม่พบมีการระบาด แต่หน่วยงานที่รับผิดชอบมีมาตรการควบคุมและเฝ้าระวังโรคนี้อยู่

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Abstract : Wirawat Chaya, Peerasak Chantaraprateep, Virat Sumateewatanakul, Kitti Virutudomsin, Sangchai Thitichankamol. 2000. Nipah virus encephalitis : A new emergent zoonotic disease. Thai J Hlth Resch 14 (2) : 131-138.

During late September 1998 to June 1999, an epidemic outbreak of suspected Japanese Encephalitis occured among pig farmers and slaughterhouse workers who directly contacted with infected pigs in Malaysia and Singapore respectively. However, it was found later that the true causative pathogen was a Hendra-like paramyxovirus named Nipah virus. The outbreak was first reported in Kinta, Perak State of Malaysia, but the virus was first isolated from patients living in Sungai Nipah Village, Negri Sembilan State. Totally, over 265 patients were diagnosed including 105 deaths in Malaysia, and 11 cases with one death in Singapore. Most patients had some clinical signs such as fever, headache, dizziness, vomiting and reduced consciousness. The distinctive neurological signs were segmental myoclonus, areflexia and hypotonia, hypertension and tachycardia. Cerebrospinal fluid and serum examinations were positive for Nipah virus. Death was probably due to severe brainstem damage. Modes of transmission remain to be established. Possible natural reservoir may be the fruit bats (Island flying fox). There has still been no specific treatment or drug to cure this disease. Stringent control and prevention by culling infected pigs and routinely monitoring the virus has been imposed in Malaysia and Singapore. In Thailand, there is no report of the outbreak. However, strict measures concerning transfer of pigs across the border and regular surveillance of the disease have been implemented.

Key words : Nipah virus, encephalitis, zoonosis

Introduction

Nipah virus encephalitis is a new deadly zoonotic disease first found in Malaysia. It spread from pigs to pig farm workers, leading to mass culling of infected pigs (Chua *et al.*, 2000). The outbreak also spread to Singapore by infected pigs imported from Malaysia, and caused one death of totally 11 infected slaughterhouse workers (Lim *et al.*, 1999; Chew *et al.*, 2000). The new virus was identified as a Hendra-like paramyxovirus, and named Nipah, after the village where the virus was first isolated from the patients. This article reviews scientific literatures about this emergent zoonotic disease in aspects of etiology, epidemiology, pathogenesis, clinical signs, diagnosis, treatment, control and prevention.

Etiology

The virus was first isolated from cerebrospinal fluid of patients admitted at Seremban Hospital in Malaysia. Initially, serological tests confirmed Japanese Encephalitis infection in many cases. However, according to epidemiological evidence, it implied that another virus might involved. Chua and his colleagues (1999) found that the virus caused syncytial formation in Vero cells. The virus samples were then identified at the Center for Disease Control (CDC), Fort Collins, U.S.A. Electron microscopic examination showed pleomorphic viral particles in both spherical and filamentous forms, 200-300 nm in diameter and 10,000-10,040 nm in length. The helical nucleocapsids were seen within the envelope. Viral morphogenesis occurred at the cell membrane of host multinucleated cells. The new virus was compatible with paramyxovirus and cross-reacted with Hendra virus antibody by immunofluorescence (Chua *et al.*, 2000).

The genome of Nipah virus is single stranded RNA with 15,200 - 15,900 nucleotides. Phylogenetic study indicated that Nipah virus is not completely identical but closely related to Hendra virus (the virus that killed 13 horses and two horse trainers in Queensland, Australia) (Harcourt *et al.*, 2000).

Epidemiology

It has been hypothesised that the disease emerged after the death of two horses, followed by the death of pig farm workers in Ampang Perak in 1997. The workers were diagnosed with viral encephalitis. In 1998, mild disease in pigs and mortalities in man were reported. The outbreak occured in Sikamat, Sungai Nipah, Ipoh, and Bukit Pelandak. Until mid June 1999, there were more than 265 people of viral encephalitis including 105 deaths

in Malaysia. (Chua *et al.*, 2000 ; Parashar *et al.*, 2000). Mean age of the patients was 37 years. The ratio of male to female patients was 4.5:1. In Singapore, 11 cases with one death were reported. All victims were abattoir workers who directly contacted with live infected pigs imported from Malaysia (Chew *et al.*, 2000).

Positive results of serological analysis for Nipah virus antibody were found in horses, dogs, cats, and goat. Furthermore, Chua and his team discovered the virus in urine samples collected from the Island flying fox or large fruit bats (*Pteropus hypomelanus*). They suggested that this creature might be a possible natural reservoir since the bats could migrate and spread the virus.

Modes of transmission study in pigs by researchers at the Australian Animal Health Laboratory (AAHL), CSIRO, Australia, indicated that incubation period for clinical signs was 14-16 days and 7-10 days in animals with oral and parenteral inoculation respectively. In-contact pigs developed clinical signs very quickly. Virus was found in tonsils and respiratory epithelium. Human-to-human transmission has not been reported (Parashar *et al.*, 2000).

Clinical signs and pathological findings

Pigs

Generally, morbidity is high but mortality is low. Disease in piglets has not been unequivocally reported. Weaners and growers may develop acute fever (39.9 degree celsius) and forced respiration. Mortality increases for the first 7-10 days in weaners. Disease is more severe in adult pigs, including breathing difficulty with blood tinged mucus or frothy discharge dripping from nose.Neurological signs in sows are head pressing or head shaking, biting behavior, trembles, muscle fasciculation, tetanic spasm, and convulsions. Sow may develop abortion or give stillborn piglets. Pigs with respiratory distress may die in 2-3 days. Postmortem findings shows varying degrees of consolidation of lung, exudate in bronchi and kidney congestion (Ng,1999)

Humans

The main clinical signs are fever, headache, dizziness, vomiting and a reduced level of conciousness (Chua *et al.*, 1999). Some patients may develop only respiratory symptoms without any signs of encephalitis (Lee *et al.*, 1999 ; Chew *et al.*, 2000). Typical neurological signs include segmental myoclonus affecting the diaphragm limbs, areflexia and

hypotonia, hypertension and tachycardia which determine pathophysiology of brainstem and upper cervical spinal cord (Goh *et al.*, 2000). Severe damage of the brainstem may lead to death. The important pathological change is vasculitis in small blood vessels such as arterioles, capillaries and venules in brain. Thrombosis and infarction are results in severe brain damage. Magnetic resonance imaging (MRI) scans of the brain may reveal the multiple scattered small white matter lesions (Chua *et al.*,1999 ; Lee *et al.*,1999 ; Lim *et al.*, 1999; Lim *et al.*, 2000). Vasculitis-induced thrombosis may also be found in lung, heart and kidney. The virus will cause endothelial syncytial formation and its inclusion bodies may be present in brain. Other laboratory findings may include low lymphocyte count, low serum sodium , and high aspartate aminotransferase concentration. Cerebrospinal fluid protein and white blood cell count may be high (Paton *et al.*, 1999).

Diagnosis

The virus can be isolated from tissue samples of necropsied animals e.g. lung, liver, kidney, spleen, heart and brain, cultured in Vero cells and examined by electron microscope. Serological test for IgM antibodies against Hendra virus is also useful (Chua *et al.*, 1999 ; Goh *et al.*, 2000).

Differential diagnosis

Japanese Encephalitis (JE)

JE is a mosquito-borne viral disease. The transmission occures mainly in Eastern and Southeastern Asia. The disease is usually seasonal depending on the prevalence of its vectors, mosquitoes. JE mostly affects children and mortality rate is about 20-30 %. Clinical signs in humans include headache, fever, gastrointestinal symptoms, confusion and disturbances in behavior, encephalitis. The illness may be fatal (one-third), another one-third survive with serious neurologic after-effects and the remaining one-third of cases recover without further problems. Generally, pigs are not sick. Sows may abort or labor to stillborn piglets. Virus morphology is spherical (40-60 nm in diameter) with rough surface projections covered envelope. Nucleocapsids are isometric (25-30 nm in diameter). The viral genome is linear positive-sense single stranded RNA with total length of 11,000 nucleotides. Pathology in humans includes vasculitis of blood capillaries in brain resulting in impaired blood supply (seldom be found in adults). The lesions may be diffuse or focal, but specific to cortical grey and deep grey matter.

Hendra virus (Equine morbilivirus)

Hendra virus is a virus in the family Paramyxoviridae causing new disease in many species including humans. It was first reported in Queensland, Australia, in 1994 after an outbreak of severe respiratory and neurologic disease (Murray *et al.*, 1995 ; Allworth *et al.*, 1995). Horses and humans were died with pneumonia and encephalitis respectively. Experimental studies indicated that the virus could infect horse, cat, guinea pig, rabbit and fruit bat but could not in dog, rat, mouse and chicken (Philbey *et al.*, 1998). Fruit bat may be natural reservoir of the virus, because it develop only subclinical signs, although the viral antibodies testing is positive. The disease is not highly contagious attributing to non nosocomial transmission. Most infected animals shed the virus through their urine.

Hendra virus has morphology like Nipah virus and shares some antigenic determinants, Both genomes have nucleotide homologies from 88% to 70% and predicted amino acid homologies range from 92% to 67%.

Treatment

Patients should be admitted into the intensive care unit when the severe signs have been presented, particulary for deeply comatose cases (Delikan *et al.*, 1999). The mechanical ventilator is needed for airway protection depending on degrees of severe neurological signs. Arterial thrombosis can be controlled by antithrombotic drugs such as aspirin or pentoxyfyline. An antiviral drug, ribavirin (generally used in patients with severe respiratory syncytial viral infection), was prescribed during the outbreak in Malaysia, but its clinical effect has still been unclear.

Control and prevention

The most effective prevention is to avoid contact with bodily fluids of pigs (Chew *et al.*, 2000 ; Parashar *et al.*, 2000). During the outbreak in Malaysia, infected pigs were culled and suspected to Nipah virus positive were quarantined. More than 900,000 pigs were eradicated. In Singapore, importation of pigs from Malaysia was banned. Other control measures included national surveillance program which were composed of two phases. The first one was culling of infected pigs (during the outbreak), and the second phase was serum screening test for Nipah virus. The latter has still operated until now.

In Thailand, although there is no report of the outbreak, surveillance measures concerning the transfer of pigs across the south border and routine monitoring the disease have been implemented, by the Department of Communicable of Disease Control, Ministry of Public Health and the Department of Livestock Development, Ministry of Agriculture and Cooperative.

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