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Hantavirus Infection - typical rodent-borne viral zoonosis

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INTRODUCTION

Zoonosis is a collective term for the infectious diseases transmitted from animals to humans and vice versa. Recently, various emerging infectious diseases have been identified as zoonoses. However, since the natural reservoirs for zoonosis are generally wild animals that established persistent infections without sign of disease, the eradication of zoonosis is quite difficult. An understanding of the epidemiologic and epizootiologic situation is essential, therefore, for the control and prevention of zoonosis.

Hantavirus infection is a typical zoonosis transmitted by rodents. In this paper, we briefly review the hantavirus infection and present epidemiologic and epizootiologic situation in East Asian countries.

1. Hantavirus

Hantaviruses are enveloped RNA viruses that belong

to the *Hantavirus* genus of the family *Bunyaviridae*. These viruses persistently infect their rodent reservoirs without causing disease. The virus is transmitted to humans either via the inhalation of infectious aerosols generated from contaminated animal secretions or via contaminated saliva from animal bites. Hantaviruses cause haemorrhagic fever with renal syndrome (HFRS) in Euro-Asia and hantavirus pulmonary syndrome (HPS) in North and South America [1] (Fig.1, 2).

Thus far, 22 virus species have been relegated to the *Hantavirus* genus based on the criteria of 1) more than 7% difference in amino-acid identities of the complete glycoprotein precursor and N sequences, and 2) a more than fourfold difference in two-way cross neutralization tests involving species of primary reservoir animals [2]. Each *Hantavirus* species is predominantly carried by one species of rodent [3]. Phylogenetic analysis of the hantavirus genome has demonstrated three distinct clades, each com-

Fig. 1 Diseases caused by hantavirus

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Fig. 2 Global distribution of HFRS and HPS

Fig. 3 Hantavirus and their rodent reservoirs

posed of viruses isolated from rodent hosts belonging to the same subfamily. For example, viral clades for the subfamilies *Murinae* (Old World rats and mice), *Arvicolinae* (voles and lemmings of the Northern Hemisphere) and *Sigmodontinae* (New World mice and rats) have been identified [4]. The phylogeny of the hantaviruses has been shown to mirror the genealogical relatedness of their host animals. Therefore, it has been suggested that hantavirus coevolved with their reservoir animals [5, 6]

(Fig. 3).

2. Diseases caused by hantavirus infection

Hantavirus infection causes two different forms of severe febrile disease, i.e. hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) [1]. HFRS is characterized by systemic involvement of the capillaries and small vessels, which causes capillary leakage and haemorrhagic manifestations. Renal involvement in the

form of acute renal dysfunction as a result of interstitial haemorrhage and interstitial infiltrates is also common. After the prodromal period, the clinical course of patients with severe disease can be divided into five phases: febrile, hypotensive, oliguric, diuretic and convalescent [7]. A milder type of hantavirus infection, nephropathia epidemica (NE), is caused by PUUV and occurs in northern Europe [8]. In NE patients, although renal manifestations are common, haemorrhage is rare and the five phases typical of severe HFRS are absent. The mortality of NE patients is 0.1-0.3% and is thus much lower than the 5-10% of HFRS patients infected with HTN, SEO or DOB viruses [3].

HPS is characterized by bilateral interstitial pulmonary infiltrates, respiratory compromise usually requiring the administration of supplemental oxygen and clinical symptoms resembling those of ARDS. HPS can be divided into two phases: a prodromal phase, which usually lasts 3-5 days, and a cardiopulmonary stage marked by diffuse pulmonary edema and hypotension within 2-5 days after the onset of pulmonary symptoms. The rapid progression of interstitial pulmonary edema to alveolar edema, with severe bilateral involvement and the accumulation of pleural effusion, accounts for the 30-40% mortality associated with HPS [7].

Although the characteristic symptoms of HFRS and HPS differ, increased capillary permeability is considered to be the common underlying factor of the two diseases [9-10]. Since hantavirus is usually non-cytopathogenic in cultured cells, cell-mediated immune responses, such as activation of virus specific CD8⁺ T cells and increased levels of tumor necrosis factor receptor (TNF- α), interleukin (IL)-6, and IL-10 are most likely responsible for the symptoms observed in HFRS and HPS [11].

3. Epidemiology and epizootiology of HFRS in East Asian countries

Although the total number of HFRS patients is about 60,000 - 150,000 annually, more than 90% of these cases occur in Asian countries, including China, Russia, and Korea. Epidemiologic and epizootologic information regarding the incidence of hantavirus infection in other East Asian countries is still limited, although patients with fevers of unknown etiology are suspected of being infected with hantavirus [12].

Seroepidemiological surveys confirmed hantavirus infections among humans and rodents in Taiwan [13][14], Hong Kong [15], Fiji [15], Malaysia [16], India [17], Indonesia [18], Singapore [19], Sri Lanka [20], Thailand [21-23] and Vietnam [24]. In Myanmar and Australia [15], positive sera were obtained only from humans, whereas in Cambodia only positive rodents were detected [25]. Nonetheless, taken together, the results clearly indicate that hantavirus in-

fections affect humans and rodents throughout Asia.

Positive sera, mostly to SEOV, from humans and rodents were also reported in Vietnam in 1986 [24]. Since 2001, the distribution of hantavirus infection among both human and rodents has been surveyed through collaboration between Japan and Vietnam, particularly the Core University Program conducted by Nagasaki University. Eight of 308 sera obtained from healthy people residing in the Haiphong port area and in Hanam Province, in northern Vietnam, were positive for SEOV. Four of 204 serum samples obtained from patients with fevers of unknown origin (FOU) living in the northern provinces of HaNam and ThanhHua were likewise positive. Positive sera were also detected in *Rattus* spp of rodents captured in the Haniphong port area and in HaNam and ThanhHua provinces (Dr. Truong Uyen Ninh, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam, personal communication).

A similar study has been conducted with a research group in Thailand. In Thailand, *R. norvegicus* obtained from the port area of Bangkok was reported to be infected with hantavirus, probably SEOV, transported from abroad by ship [21]. In addition, various species of inland rodents are infected with hantavirus. Amongst them, the greater bandicoot rat (*Bandicota indica*) is a major reservoir of the virus, while several species of rice-field rats, such as *R. rattus*, *Rattus exulans* and *Rattus losea*, are also natural reservoirs albeit to a lesser extent. The Thailand virus (THAIV), one of the distinct species of virus within the genus *Hantavirus*, was isolated from *B. indica* captured in a village near the western province of Kanchanaburi in 1985 [21]. Therefore, THAIV or related viruses appear to be distributed throughout Thailand. Ten of the 30 sera obtained from residents of the village where virus-infected *Bandicota* was captured showed antibody to hantavirus, which demonstrated that Thailand virus is able to infect humans. However, the virulence of THAIV towards humans has not been determined. Hantavirus has been suspected as one of the pathogens in fevers of unknown origin (FUOs) in Thailand. In the period 1999-2000, 115 cases of FOU were reported in patients admitted to Bangkok Hospital who were examined for antibodies to hantavirus. Paired sera from one patient showed high antibody titres to HTNV by IgG ELISA, IgM ELISA, and IFA test. Between 2002 and 2003, 260 paired sera from patients with FOU were collected in Surin Province. One of the sera showed a neutralising antibody titre to THAIV of 1:160, whilst the titres to HTNV and SEOV were less than 1:40. Furthermore, convalescent-phase serum did not contain hantavirus IgM antibody. Since the symptoms of the patient were comparable to those typical for HFRS, THAIV might be an additional causative agent of HFRS [23].

Conclusions

Epidemiological studies have shown that hantaviruses are widely distributed in Asia, both in humans and in rodents. Unlike the situation in Far East Asia, the number of hantavirus-antibody-positive sera has so far been quite small, even amongst FOU patients. Therefore, the significance of hantavirus infection as the causative agent for FOU in East Asia remains unclear, and further serological surveys amongst healthy people are needed. Nevertheless, these observations indicate that unidentified pathogens that cause FOU are prevalent in this region. To determine the new emerging infectious diseases which may cause FOU, the continuation of research both in humans and in animals is essential. For that purpose, projects such as the Core University Program for collaboration between Japanese institutions and those in endemic countries should be expanded.

Epizootologic studies, particularly in rodents, have confirmed the close relationship between hantavirus and animals acting as reservoirs for the virus. Since it is thought that hantaviruses coevolved with their rodent hosts, an understanding of the virus' ecology may provide unique and important information about other rodent-borne pathogens as causative agents of emerging infectious diseases.

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