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Abstract

Hantavirus; Hemorrhagic fever with renal syndrome (HFRS) is an emerging zoonotic disease in Euro-Asia which is clinically indistinguishable from leptospirosis. A total number of 1032 patients were included in the analysis from March 2013 to March 2021 with the clinical suspicion of HFRS-like illness. Of them, 168 patients were positive for hantavirus IgM antibodies. Thirty-one patients out of 35 patients had given a four-fold rise IgG antibody titre with paired serum confirming the acute hantavirus infections. Detected antibodies showed a diverse pattern, strongly cross-reacting with Seoul, Hantaan and Puumala virus antigens. All the IgM positive patients had no serological evidence of acute dengue or leptospirosis and had classical features of HFRS; fever, thrombocytopenia and renal involvement. More than 90% of patients had a history of rodent exposure 2-3 weeks prior to the onset of the fever. The highest number of positive cases were diagnosed from the Western and North-Central Provinces of Sri Lanka during the paddy harvesting seasons. A significant number of patients had developed severe complications with a high mortality rate. Therefore, hantavirus infection should be considered as a differential diagnosis for leptospirosis-like illness in Sri Lanka.

Text

Hantavirus disease is an emerging zoonotic infection. Hantaviruses cause two classical clinical presentations in humans: Hemorrhagic Fever with Renal Syndrome (HFRS) in Euro-Asia and Hantavirus Cardiopulmonary Syndrome (HPS/HCPS) in North and South America (1). Nephropathia Epidemica is a mild form of HFRS caused by Puumala viruses in north Europe. In addition, infections with mixed clinical features and atypical clinical presentations also have been reported world-wide (2,3).

HFRS is clinically presented with fever, thrombocytopenia and renal involvement. Hantaan, Seoul, Dobrava and Puumala are the main viruses that cause HFRS. The outcome of the disease varies from self-limited, moderate to severe, and the motility rate depending on the virus strains and host immune factors (4,5).

The first report on hantavirus in Sri Lanka was published in 1988 indicating seropositivity in febrile patients and rats in port area(6). Since then, few studies have been conducted to detect the hantavirus infections in selected geographical areas in Sri Lanka, including patients with leptospirosis-like illnesses, infections with pulmonary symptoms and the association with the occurrence of chronic kidney disease of unknown aetiology (7-11). So far, seropositivity to the Hantaan, Puumala-like, Thailand-like, and Seoul viruses has been reported in isolated settings. From 2008 to 2011, increased incidence of leptospirosis-like illnesses were reported, and the majority were clinically diagnosed as leptospirosis (12). However, only less than 50% of these cases were laboratory confirmed (12). HFRS often mimic leptospirosis with clinical manifestation and preliminary laboratory investigation results, requiring laboratory confirmation. But, the availability of laboratory diagnostic facilities for hantavirus in the country is limited.

Therefore, a considerable number of HFRS cases were under-reported. This report describes the clinical features and epidemiology of hantavirus infection with HFRS in recent years.

Clinically suspected patients with HFRS/HFRS-like infections referred for diagnosis of hantavirus infections from March 2013 to March 2021 were included in the analysis. Case definition was based on clinical features of HFRS - fever, thrombocyropenia and any sign/ symptom suggestive of renal involvement according to the International Classification of Diseases (ICD 10). Acute phase and, when available, convalescent-phase blood samples of 10-14 days apart were collected. Acute-phase blood samples were analysed for anti-hantavirus IgM using locally validated commercial enzyme-linked immunosorbent assay based on recombinant nucleocapsid antigens (Anti-Hanta Pool 1 "Eurasia" IgM ELISA, Euroimmune, Germany, Cat.No.EI278h-9601-1M), immune-fluorescent assays on acetone fixed virus infected cells (PUU IgM, DOB/HTN IgM IFA, Progen, Germany Cat.No.PR77056/PR77065), and IgM/IgG immunochromatographic assay containing recombinant antigen, (SD BioLine Hantaan ICT, SD Diagnostics, Korea, Cat.No.17FK10) followed by IgM ELISA/ IFA depending on the availability, following manufactures' instructions on protocol, cut-off values and result interpretations. Both acute and convalescent blood samples were tested for anti-hantavirus IgG titre using locally validated commercial IFA (BOB/HTN IgG IFA, Progen, Germany, Cat.No.PR77056). In addition, patients' clinical and demographic data were analysed. All hantavirus IgM positive samples were tested for dengue NS1 antigen, anti-dengue IgM antibodies to exclude acute dengue virus infections and anti-leptospira IgM or microscopic agglutinin test (MAT) to diagnose leptospirosis. Ethical clearance was obtained from Medical Research Institute, Sri Lanka (MRI/ERC/13/2013), concent was not required for each patient.

A total number of 1032 (604 males , 428 females) clinically suspected HFRS/HFRS-like patients were included in the analysis. Of them, 168 (16.28%) patients were positive with anti-hantavirus IgM antibodies, including 109 males and 59 females. There was no statistically significant difference between genders for being positive with hantavirus IgM (p=0.068, Chi-square test). Only 35 convalescent samples were able to collect from the anti-hantavirus IgM positive patients, and a four-fold rise of anti-hantavirus IgG antibodies was detected in 31 (88.57%) of those patients. In addition, detected antibodies were given diverse patterns, giving strong positive results for different hantavirus antigens, including Seoul, Hantaan and Puumala virus. Blood investigations showed that 85.80 % of diagnosed patients had Leukocytosis (139/162), and 80.19% (81/101) had elevated CRP.

All hantavirus IgM antibodies positive serum was negative for serological evidence of acute dengue or leptospira infections.

All the anti-hantavirus IgM antibodies positive patients had fever, thrombocytopenia and at least one feature of renal involvement showing the classical HFRS clinical features. Commen clinical features and complications developed are given in Table 1. Of the hantavirus IgM antibody-positive patients, 29 (17.3%) deaths were reported, and the majority was (19/29) due to multi-organ failure following acute renal failure. Other causes of death were given in Table 1. Motility rate was significantly higher in the Hantavirus IgM positive group compared to the negative group (p=0.009, Chi-square test).

The distribution of the hantavirus infection positive cases among the nine provinces in Sri Lanka is shown in Fig. 1.

The majority (151/168) of the patients had given a significant history of exposure to rodents, and 72.0 % of patients had develop symptoms 2-3 weeks after paddy harvesting activities, often reported as small outbreaks in February to March. Other exposures are shown in Table 1.

According to our data, hantavirus infection has a countrywide distribution with the highest in Western and North Central Provinces in paddy harvesting season. Due to lack of diagnostic facilities, reported HFRS cases were limited to few studies in the past and this report indicate siginificat number of cases in recent years with the improvement and the availability of diagnostic facilities in the country (6,8,9,11). Yoshimatsu *et al.* shown high seroprevalence to the Thailand Orthohantavirus or an antigenically related virus in Giradurukotte area in 2019 indicating past exposure to the hantavirus (7). And these patients may be asymptomatic at the infected time or clinically misdiagnosed. Furthermore, the number of HFRS incidences may be increased due to the increased human exposure and increased rodents' population due to unplanned urbanisation, deforestation, unplanned garbage disposal, and changes in agriculture practices.

Although it cannot precisely state the causative type of the virus with IgM or IgG assays due to the antigenic cross-reactivity among hantaviruses and the ability of the kits to detect multiple types of Euro-Asian Hantaviruses, it is quite evident that multiple distinct types are circulating in the country. Serological evidence of Hantaan, Seoul and Puumala-like and Thailand-like viruses in humans were reported before in different parts of the country, and our data shows a similar pattern (6-11). Recently, novel mouse-borne and rat-borne orthohantavirus species and their resovoirs were identified in the country (13).

Rising IgG antibody titer against hantavirus infection was detected in 31 out of 35 IgM positive patients confirming diagnosis; remaining hantavirus IgM antibody-positive patients were unable

to be confirmed as acute or recent past infection due to the unavailability of the convalescent samples. Although IgM antibodies against hantavirus can be detected up to 3-4 months following acute infection, considering clinical features and exclusion of acute leptospiral infection in this group gives strong evidence that hantavirus was the probable causative agent for this clinical presentation. None of the patients had evidence of acute leptospirosis in hantavirus IgM positive patients, excluding co-infections which was reported previously (9). There were 29 deaths with serious complications in the sero-positives resulting case fatality rate of 17%. Clinical features of HFRS were similar to leptospirosis, and therefore laboratory confirmation is vital to assess disease burden in the country.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Figure legends

Fig.1. : Hantavirus IgM positive cases distribution among nine provinces in Sri Lanka. Number of positive cases detected in each province was indicated.

Table 1. Clinical features, complications, fatality and exposure to rodents among hantavirus IgM positive patients

Clinical features, complications and exposures	**No. of patients out of 168 hantavirus IgM positive patients**
Myalgia	129 (76.8%)
Liver involvement/Hepatitis	65 (38.7%)
Difficulty in breathing	41 (24.4%)
Acute renal failure	51 (30.4%)
Bleeding manifestation	49 (29.2%)
Non cardiac pulmonary edema	27 (16.0%)
Multi-organ failure	27 (16.0%)
Massive haemorrhage	9 (5.4%)
Myocarditis	8 (4.8%)
Encephalitis	2 (1.1%)
Fatality Due to multi-organ failure following ARF circulatory failure cardiac failure respiratory failure fulminant hepatitis CNS involvement unknown	29 (17.3%) 19 3 2 2 1 1 1
Exposure to rodents during paddy harvest during paddy cultivation and processing at construction sites at storage facilities during military activities house-hold infest with rats	151 (89.88%) 121 20 4 2 2 2
Average age (years) male female	 41.4 36.2

ARF- acute renal failure

CNS- central nervous system

Figure 1 : Hantavirus IgM positive cases distribution among the provinces in Sri Lanka.