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Epidemiology Communication

Hantavirus Hemorrhagic Fever with Renal Syndrome - Suspected Cases in Sri Lanka: Clinical Picture and Epidemiology from 2013–2021

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ABSTRACT: Hantavirus hemorrhagic fever with renal syndrome (HFRS) is an emerging zoonotic disease in Europe and Asia, which is clinically indistinguishable from leptospirosis. A total of 1,032 patients with clinical suspicion of HFRS-like illness were included in the analysis from March 2013 to March 2021. Of these, 168 were positive for hantavirus immunoglobulin M (IgM) antibodies. Thirty-one of 35 patients had a 4-fold increase in IgG antibody titer with paired serum, confirming acute hantavirus infections. The detected antibodies showed a diverse pattern, strongly cross-reacting with the 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, including 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 was diagnosed in the Western and North Central Provinces of Sri Lanka during the paddy harvesting seasons. A significant number of patients develop severe complications with high mortality rates. Therefore, hantavirus infection should be considered as a differential diagnosis for leptospirosis-like illnesses in Sri Lanka.

Hantavirus disease is an emerging zoonotic disease. Hantaviruses cause two classical clinical presentations in humans: hemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus cardiopulmonary syndrome (HPS/HCPS) in North and South America (1). Nephropathia epidemica is a mild form of HFRS caused by the Puumala virus in Northern Europe. In addition, infections with mixed clinical features and atypical clinical presentations have been reported worldwide (2,3). HFRS presents clinically with fever, thrombocytopenia, and renal involvement. Hantaan, Seoul, Dobrava, and Puumala are the main viruses causing HFRS. The outcome of the disease varies from self-limiting to moderate to severe, and the mortality rate depends on the virus strains and host immune factors (4,5).

The first report of hantavirus in Sri Lanka was published in 1988, indicating seropositivity in febrile patients and rats in port areas (6). Since then, few studies have been conducted to detect hantavirus infections in selected geographical areas in Sri Lanka, including patients with leptospirosis-like illnesses, infections with pulmonary symptoms, and association with the occurrence of chronic kidney disease of unknown etiology (7–11). So far, seropositivity to the Hantaan, Puumala-like, Thailand-like, and Seoul viruses has been reported in isolated settings. An increased incidence of leptospirosis-like illnesses was reported from 2008 to 2011, and the majority were clinically diagnosed with leptospirosis (12). However, only less than 50% of these cases are laboratory confirmed (12). HFRS often mimics leptospirosis, with clinical manifestations and preliminary laboratory investigation results requiring laboratory confirmation. However, the availability of laboratory diagnostic facilities for hantaviruses in Sri Lanka is limited. Therefore, a considerable number of HFRS cases have been underreported. This report describes the clinical features and epidemiology of HFRS caused by hantavirus infection in recent years.

Clinically suspected patients with HFRS/HFRS-like infections referred for the diagnosis of hantavirus infection from March 2013 to March 2021 were included in the analysis. Case definition was based on clinical features of HFRS - fever, thrombocytopenia, and any sign/ symptom suggestive of renal involvement according to the International Classification of Diseases (ICD 10). Acute phase and, when available,

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

Clinical feature, complication and exposure	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 (ARF)	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	29 (17.3)
Due to multi-organ failure following ARF	19
circulatory failure	3
cardiac failure	2
respiratory failure	2
fulminant hepatitis	1
CNS involvement	1
unknown	1
Exposure to rodents	151 (89.88)
during paddy harvest	121
during paddy cultivation and processing	20
at construction sites	4
at storage facilities	2
during military activities	2
house-hold infest with rats	2
Average age (yr)	
male	41.4
female	36.2

CNS, central nervous system.

convalescent-phase blood samples were collected 10–14 days apart. Acute-phase blood samples were analyzed for anti-hantavirus IgM using a locally validated commercial enzyme-linked immunosorbent assay (ELISA) based on recombinant nucleocapsid antigens (Anti-Hanta Pool 1 "Eurasia" IgM ELISA, EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany, Cat.No.EI278h-9601-1M), immunofluorescent assays (IFA) on acetone-fixed virus-infected cells (PUU IgM, DOB/HTN IgM IFA, PROGEN Biotechnik GmbH, Heidelberg, Germany; Cat.No.PR77056/PR77065), and IgM/IgG immunochromatographic assay containing recombinant antigen (SD BioLine Hantaan ICT, SD Diagnostics Inc., Yongin, Korea; Cat.No.17FK10) followed by IgM ELISA depending on the availability, following the manufacturer's instructions on protocol, cut-off values, and result interpretations. Both acute and convalescent blood samples were tested for anti-hantavirus IgG titers using locally validated commercial IFA (BOB/HTN IgG IFA, PROGEN Biotechnik GmbH; Cat.No.PR77056). In addition, patients' clinical and demographic data were analyzed. 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 to diagnose leptospirosis. Ethical clearance was obtained from the Medical Research Institute of Sri Lanka (MRI/ERC/13/2013), and consent was not required for each patient.

A total number of 1,032 (604 men, 428 women) clinically suspected patients with HFRS/HFRS-like were included in the analysis. Of these, 168 (16.28%) patients were positive for anti-hantavirus IgM antibodies, including 109 men and 59 women. There was no statistically significant difference between sexes for being positive for hantavirus IgM (P = 0.068, chi-square test). Only 35 convalescent samples were collected from the anti-hantavirus IgM-positive patients, and a 4-fold increase in anti-hantavirus IgG antibodies was detected in 31 (88.57%) of those patients. In addition, the detected antibodies showed diverse patterns, giving strong positive results for different hantavirus antigens, including Seoul, Hantaan,

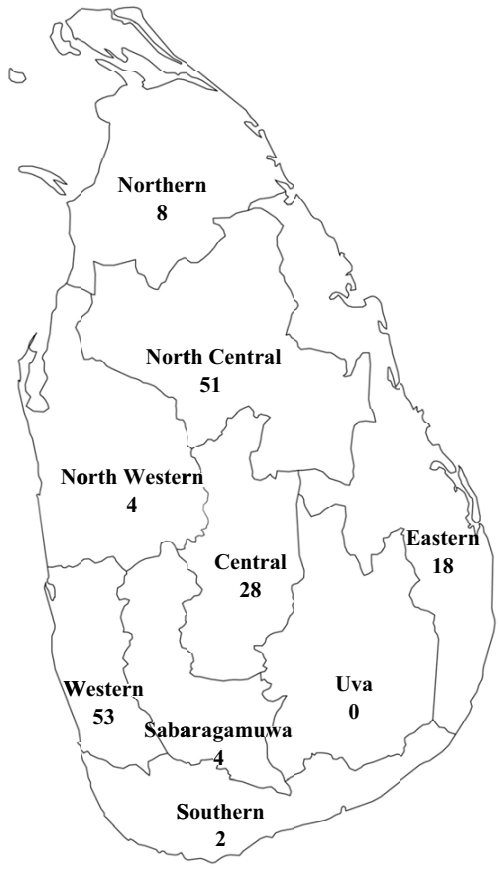

Fig.1. Hantavirus IgM-positive cases distribution among 9 provinces in Sri Lanka. The number of positive cases detected in each province was indicated.

and Puumala viruses. Blood investigations showed that 85.80% of diagnosed patients had leukocytosis (139/162), and 80.19% (81/101) had elevated C-reactive protein.

All serum samples positive for hantavirus IgM antibodies were negative for serological evidence of acute dengue or leptospira infection. All anti-hantavirus IgM antibody-positive patients had a fever, thrombocytopenia, and at least one feature of renal involvement showing classical HFRS clinical features. The clinical features and complications that developed in the patients are shown 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. The other causes of death are listed in Table 1. In addition, the mortality rate was significantly higher in the hantavirus IgM-positive group than that in the hantavirus IgM-negative group (P = 0.009, chi-square test). The distribution of hantavirus infection-positive cases among the 9 provinces of Sri Lanka is shown in Fig. 1.

The majority (151/168) of the patients had a significant history of exposure to rodents, and 72.0% of patients had developed symptoms 2–3 weeks after paddy harvesting activities, often reported as small outbreaks from February to March. Other exposures are listed in Table 1. According to our data, hantavirus infection has a countrywide distribution, with the highest prevalence in Western and North Central Provinces in the paddy harvesting season. Due to the lack of diagnostic facilities, the reported HFRS cases were limited to a few studies in the past. This report indicates a significant number of cases in recent years with the improvement and availability of diagnostic facilities in the country (6,8,9,11). Yoshimatsu et al. showed high seroprevalence to the Thailand orthohantavirus or an antigenically related virus in the Giradurukotte area in 2019, indicating past exposure to hantavirus (7). These patients may be asymptomatic at the time of infection or clinically misdiagnosed. Furthermore, the incidence of HFRS may be increased due to increased human exposure and rodent population due to unplanned urbanization, deforestation, unplanned garbage disposal, and changes in agricultural practices.

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

Rising IgG antibody titers against hantavirus infection were detected in 31 out of 35 IgM-positive patients confirming a diagnosis. The remaining hantavirus IgM antibody-positive patients could not be confirmed as acute or recent past infections due to the unavailability of convalescent samples. Although IgM antibodies against hantavirus can be detected for up to 3–4 months following acute infection, considering the clinical features and exclusion of acute leptospiral infection in this group provides strong evidence that hantavirus is the probable causative agent for this clinical presentation. None of the hantavirus IgM-positive patients had evidence of acute leptospirosis, excluding co-infections that were reported previously (9). There were 29 deaths with serious complications in the sero-positives resulting case fatality rate of 17%. The clinical features of HFRS are similar to those of leptospirosis; therefore, laboratory confirmation is vital to assess the disease burden in the country.

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Conflict of interest None to declare.

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