Haemorrhagic Fever with Renal Syndrome in Singapore

Dear Editor,

Hantaviruses are enveloped negative stranded RNA viruses (family *Bunyaviridae*, genus *Hantavirus*) transmitted to humans via aerosols or direct contact from inapparent infection from rodents of the Muridae and Cricetidae families. Two distinct clinical forms are recognised: haemorrhagic fever with renal syndrome (HFRS), a severe acute febrile illness with renal and hepatic dysfunction found in Eurasia[1,2] and hantavirus cardiopulmonary syndrome (HCPS) found in the Americas.[1] In contrast to China and South Korea, where annual incidence of HFRS reaches more than 11,000 and 300 cases respectively,[1,3] reports of human HFRS in Southeast Asia are lacking. We report 2 patients with HFRS in Singapore who had frequent travel to Malaysia.

Case Reports

Patient A, a previously healthy 42-year-old Malaysian Chinese man was admitted to Tan Tock Seng Hospital in May 2010 with fever, myalgia and lethargy for 3 days. He was a construction site supervisor in Singapore but frequently returned to Johor Bahru, Malaysia for the weekend. On admission, the patient was febrile (38.9°C). He had petechiae over bilateral ankles. A complete blood count showed marked thrombocytopenia (13 x10^9 cells/L) and lymphopenia (0.6 x10^9 cells/L) without leukocytosis (6.2 x10^9 cells/L). Four days into admission, his fever had settled but the patient had abdominal bloating and dyspnoea without hypoxia. Acute renal failure (peak creatinine 520 µmol/L) had developed with relative oliguria (0.85 L/24h) and severe transaminitis (aspartate aminotransferase 911 U/L, alanine aminotransferase 466 U/L). Urinalysis showed microscopic haematuria. Ultrasound examination showed bilateral pleural effusions, ascites and mildly increased renal echogenicity. Six days after admission, the patient's condition improved. He had increased urine output (3 L/24h) with gradual recovery of renal and liver function. He was discharged after 11 days. His renal function normalised at 6-months follow-up.

Patient B, a 35-year-old Singaporean Chinese man was admitted in October 2010 after experiencing fever, myalgia, nausea, abdominal pain and vomiting for 1 week. He was an office worker but had multiple visits to Kuala Lumpur and Johor Bahru, Malaysia for leisure. His examination was unremarkable except for temperature of 39°C. Initial blood results showed thrombocytopenia (92 x10^9 cells/L) and lymphopenia (0.6 x10^9 cells/L). Results of renal function tests were within normal limits. Five days after admission, he had dyspnoea and generalised oedema. Physical examination showed anasarca, ascites and pleural effusions but vital signs remained stable. Computed tomographic scan of the abdomen showed mild ascites and pleural effusions. An elevated creatinine (290 µmol/L), proteinuria (1+) and mild transaminitis were noted. His condition improved and he was discharged after 10 days. His renal function at 2 weeks after discharge was within normal limits.

Laboratory confirmation was performed at the Environmental Health Institute, a public health laboratory. Immunoglobulin M (IgM) and immunoglobulin G (IgG) against hantavirus were detected by enzyme-linked immunosorbant assay (ELISA, Focus diagnostics, USA) in both patients' acute-phase serum samples according to manufacturer's instructions. Convalescent-phase serum samples showed 4-fold rise in hantavirus IgG (patient A) and IgM (patient B) titers suggesting recent infection. The viral RNA, however was not detectable in the acute-phase blood samples by reverse transcription-PCR (RT-PCR) targeting the L segment of all hantaviruses.[4] Other serologic tests for dengue, leptospirosis, viral hepatitis, human immunodeficiency virus, rickettsial diseases and repeated blood films for malaria were negative. Blood, urine and leptospiral cultures were also negative.

Joint epidemiological investigations by the Ministry of Health and the National Environmental Agency were unable to determine a local source of the infection as both patients had no reported close encounter with rodents.

Discussion

We describe 2 clinical cases of HFRS in Singapore. The last reported human case in Singapore was 14 years previously in 1996.[5] An older serosurvey in 1989 of 4 distinct patient groups with suspected dengue, hepatitis, leptospirosis and nephritis showed hantavirus seroprevalence of 2% to 8%.[6] Despite the lack of diagnosed human cases, 2 reports have established the seroprevalence of hantavirus in the wild rodent population of Singapore to be 26% to 34%.[4,6] Among *Rattus norvegicus* and *R. tanezumi diardii*, the predominant

rodent species in Singapore, positive hantavirus RT-PCR was found in 2.24%.[4] Sequence analysis established 2 genetically different hantavirus strains: Seoul virus strain Singapore circulating in *R. norvegicus* and Serang virus strain Jurong circulating in *R. tanezumi diardii*.[4] While the pathogenicity of Serang virus remains unknown, the clinical presentation of both patients was compatible with Seoul virus infection which is responsible for a moderate form of HFRS.[1] Vascular permeability remains the hallmark of HFRS. Although not fully understood, viral replication together with immune response has been postulated to result in tissue injury.[1] Manifestations of haemorrhagic complications, pleural and abdominal effusions, oliguria and renal failure of Seoul virus infection are milder compared to the more severe HFRS form caused by Hantaan virus found in Russia, China and South Korea and has a lower mortality of less than 1%.[1] It is possible these milder symptoms may contribute to the diagnosis of HFRS being missed locally. A repeated serosurvey of Singapore residents may help to assess current disease burden in view of urbanisation and changing environmental exposure.[6]

Elsewhere in Southeast Asia, hantavirus infections have been reported in rodents and humans. In Malaysia, 15.9% of 87 rodent samples from Port Klang were positive for hantavirus antibody as were 2.5% of serum samples from 119 patients with chronic renal failure at a university hospital in Kelantan.[7] Of 655 rodents captured in 7 port areas of Indonesia, 24 of 238 *R. norvegicus* and 1 of 102 *R. exulans* from Sulawesi island and 1 of 142 *R. rattus* from Java island had antibodies against hantavirus.[8] During a dengue epidemic in Central Java, Indonesia, 8% to 11% of febrile patients initially suspected of dengue virus infection but with negative dengue-virus serology had evidence of recent hantavirus infection.[9,10] In Thailand, seroprevalence of hantavirus in rodents has ranged from 2.1% in northeastern provinces,[11] 2.3% to 4% in central plateau areas[12] to 24% near Bangkok.[13] A subsequent study of 260 patients clinically diagnosed with leptospirosis but serologically negative for leptospiral antigens had one patient with high titers of hantavirus-reactive IgM and IgG.[14]

Conclusion

Since serological diagnosis of hantavirus infection in humans is not routinely offered in this region, it is likely that HFRS is underestimated. Because rodent reservoirs do exist with significant seroprevalence of hantavirus infection, clinicians should remain alert to the diagnosis of HFRS in febrile patients presenting with renal and hepatic dysfunction. This report highlights a possibly overlooked viral zoonosis in Singapore, and probably the rest of Southeast Asia.

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