HANTA VIRUS INFECTION: A CASE REPORT FROM INDIA

The clinical presentation of hantavirus infections in India is unclear. We report here a case of hantavirus infection in a 46 year old quarry worker presenting with fever, abdominal pain, jaundice, thrombocytopenia and renal dysfunction. Seroconversion and rising anti-hantavirus IgG titers were taken as evidence of hantavirus infection. Clinicians should consider hantavirus infections in the differential diagnosis of acute febrile illness along with scrub typhus, leptospirosis and dengue.

Key words: Hantavirus, India, renal disease

Hantaviruses are rodent-borne viruses (roboviruses) that cause two important disease syndromes; hemorrhagic fever with renal syndrome (HFRS) in Europe and Asia and hantavirus cardiopulmonary syndrome in America.[1] HFRS refers to a group of clinically similar illnesses accompanied with renal dysfunction and caused by Hantaan virus (HTNV), Seoul virus (SEOV), Dobrava virus(DOBV) and Thailand virus(THAI).[2] Although hantaviruses have a widespread geographical distribution, no hantavirus case has been reported from India, which is the place of origin of the Thottapalayam virus (TPMV), one of the most divergent hantaviruses.[3,5] Absence of case documentation and studies on
hantaviruses in India may be due to many reasons. Probably the most important of them is the absence of diagnostic kits, which, if commercially available, are exorbitantly priced. Some serotypes are also considered liable to be used for bio warfare. These constraints impede productive collaborations between laboratories in different geographical regions willing to pursue hantavirus research. In addition, clinicians in non-endemic areas are unfamiliar with the clinical features of hantavirus infections, which can be non-specific and require laboratory confirmation. We present a case of a patient who was diagnosed to have hantavirus infection based on clinical and serological criteria.

Case Report

The patient (07/D-316), a 46-year-old male quarry worker from Cudappah in Andhra Pradesh, India, was admitted to the medicine ward of the Christian Medical College, Vellore, on 12 February 2007. He presented with a history of high-grade fever, jaundice for 8 days, abdominal pain and loose stools for 5 days. On physical examination, the patient was febrile (temperature 104°F), icteric, tachycardic with pallor and jaundiced. He was a regular consumer of alcohol with dependence. He had no rash, eschar or overt bleeding. He was also found to have mild hepatosplenomegaly. He also gave complaints of being oliguric for 2 days. No information on exposure history indicating whether the patient had been in contact with rodents through farming, trapping or through cleaning of rodent-infested areas was recorded.

Investigations performed on the day of admission and 6 days after onset of illness revealed pancytopenia (haemoglobin–5.9%), a white blood cell count of 1900 cells/mm$^3$ and a platelet count of 87,000 cells/mm$^3$. The presence of band forms and giant platelets was also noted. The activated partial thromboplastin time was 44.0 seconds indicating whether the patient had been in contact with rodents through farming, trapping or through cleaning of rodent-infested areas was recorded.

Elevated serum creatinine (4.9 mg%) and urea (128 mg%) levels suggested renal failure. Urinalysis revealed proteinuria (3+), haematuria (15–20 red blood cells per high power field) and presence of coarse and fine granular casts. Liver function tests revealed hyperbilirubinaemia and hypoalbuminaemia [total bilirubin–2 mg%, albumin–2.7 mg%, alanine aminotransferase (ALT)–17 U/ml]. The lactate dehydrogenase level was elevated at 722 U/L. Elevated creatine phosphokinase CPK- 3444 μ/L and serum phosphorus (7.4 R) levels were also recorded. Three blood cultures and bone marrow aspirate cultures were sterile. His bone marrow smear revealed moderate megaloblastic charges. His chest X-ray was normal. Investigations performed for leptospirosis (IgM ELISA, Pan Bio, Brisbane, Australia), scrub typhus (IgM ELISA, Pan Bio), typhoid fever (Typhidot, MBDr, Selangor, Malaysia), dengue (Pan Bio Rapid Cassette Test), malaria, and blood culture were negative.

He was treated with ceftriaxone daily and doxycycline twice daily for 1 week. He was also given methylcobalamin injections and folic acid supplements. He became afebrile in the ward and was discharged with a diagnosis of acute undifferentiated febrile illness and megaloblastic anaemia with pancytopenia. Convalescent sample was collected on 08.03.07.

Blood samples (acute and convalescent) were subsequently tested for anti-hantavirus immunoglobulin IgM and IgG. Polymerase chain reaction (PCR) analysis of the RNA extract from the buffy coat sample targeting the S genome segment of hantaviruses was negative. Acute phase sample was positive for hantavirus IgM by enzyme-linked immunosorbent assay (ELISA) (Focus Technologies, Cypress, CA USA, 1 in 100 dilution) and immunofluorescence assay IFA (HTNV, 1 in 10 dilution) but negative for anti-hantavirus IgG antibodies. Convalescent sample of the patient showed high levels of anti-hantavirus IgG both by ELISA (1 in 100 dilution) and by (IFA,1 in 10 dilution). The IFA slides spotted with HTNV were gifted by Dr. Jiro Arikawa, Institute for Animal Experimentation, Graduate School of Medicine, Hokkaido University, Sapporo, Japan. Evidence of hantavirus infection was seroconversion and rising titres of hantavirus-specific IgG in the convalescent sample.

Discussion

Classical HFRS has an incubation period ranging from 4 to 42 days. High fever, flushing of the face, myalgia, headache, conjunctival suffusion, petechial rash, nausea, vomiting and abdominal pain are a few early symptoms of HFRS. For convenience, it is described in five clinical phases: febrile, hypotensive, oliguric, diuretic and convalescent. However, these phases may overlap in mild and moderate cases. In classical cases, thrombocytopenia is most severe by day 9 and thereafter begins to resolve. Evidence of renal failure is seen by day 5 of the illness when it peaks and thereafter starts resolving. The case presented above follows the typical course of HFRS, with thrombocytopenia and renal manifestations.

Apart from HFRS cases presenting with renal symptoms, undifferentiated febrile illness has been described as one of the protein manifestations of HFRS where patients have thrombocytopenia and elevated ALT values but no renal disease. However, thrombocytopenia is no longer considered a characteristic feature of HFRS. Elevated hepatic enzymes are common but do not reach high levels. In HFRS, prolonged partial thromboplastin time and left shift of leukocyte in peripheral blood smear are significant while mild renal problems (proteinuria and haematuria)
have also been reported. Gastrointestinal symptoms are also common in hantavirus infections.\(^9\,10\) Protean clinical manifestations of hantavirus infections could result in cases either being misdiagnosed or being ignored in case of mild disease with non-specific symptoms.

Injection ceftriaxone was initiated in this case to cover for bacterial infections like Gram negative sepsis, leptospirosis and enteric fever and oral doxycycline for treatment of scrub typhus. The patient did not have a therapeutic response to doxycycline as would be expected in scrub typhus. Hence, in this clinical scenario, the recovery of the patient was probably a result of the natural course of the disease rather than a therapeutic response to ceftriaxone or doxycycline.

Humans get infected by inhalation of aerosols generated from contaminated rodent excreta and saliva. The pathogenesis of HFRS is largely immunological in nature. Infection of endothelial and tubular cells and immune involvement is responsible for renal failure and thrombocytopenia seen in typical HFRS cases. Atypical lymphocytes on a peripheral smear are seen in more than 93% of the HFRS cases. The presence of immature granulocytes and giant platelets also support the diagnosis of haemorrhagic fever with renal syndrome.

Outside endemic areas, hantavirus infections may present atypically, the manifestations of disease depending on the infecting serotype. Patients with acute febrile illness presenting with thrombocytopenia, renal failure and elevated liver enzymes should be tested for anti-hantavirus IgM and IgG. Important clues for clinicians to suspect hantavirus disease include fever, headache, myalgia with proteinuria and thrombocytopenia. Because the clinical features of hantavirus infections are not pathognomonic, laboratory work-up is essential for confirmation of diagnosis. Demographics, history of animal contact and outdoor activity are important patient details to be recorded in areas non-endemic for hantavirus infections.

It has been documented that only about 20% of acute HFRS cases are positive for hantavirus RNA. This reiterates that molecular diagnosis should be used only to complement serodiagnostic assays and should not be used as the sole method of diagnosis. Reverse transcriptase PCR is not recommended for routine diagnosis because of false negatives.\(^{11}\)

In 1966, TPMV, the first indigenous Indian hantavirus species, was isolated from the spleen of a shrew (insectivore), *Suncus murinus*, captured in Vellore, South India, during field studies of Japanese encephalitis.\(^{12}\) This is one of the few hantavirus isolates from a non-rodent host.

In a study of 152 serum samples carried out at the Christian Medical College (CMC), Vellore, it was found that 23 (14.7%) individuals with febrile illness were positive for anti-hantavirus IgM and 5.7% of healthy blood donor samples tested were positive.\(^{13}\) These findings suggested the presence of hantavirus infections in the Indian population, presenting as symptomatic or asymptomatic infections. There have been reports of SEOV-like infection in 12% and Puumala virus (PUUV)-like infection in 5% of Indians presenting with a leptospirosis-like clinical picture from Cochin and Chennai areas of India.\(^{14}\) In 2007, there were reports of hantavirus infections presenting with ocular involvement from Western India.\(^{15}\) It is now proved that TPMV is phylogenetically and antigenically quite distinct from the other hantaviruses and has probably coevolved with its non-rodent host.\(^{16}\) The pathogenicity of TPMV was doubtful as the host insectivore was believed to be a spillover host. Anti-TPMV antibodies in sera from shrews in Indonesia and in a patient presenting with acute febrile illness of unknown aetiology may be proof of *Suncus murinus* being the natural host of TPMV and of causing human infections.\(^{17}\) A seroepidemiological study from CMC, Vellore, has indicated a 4% prevalence of hantavirus infections in India.\(^{17}\)

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**References**


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