Hantaviruses

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Summary

- Hantaviruses are enzootic viruses transmitted to humans by rodents.
- Symptoms: fever, flu-like syndrome followed by nephropathy, haemorrhage, hyper acute pulmonary syndrome
- A febrile patient with acute respiratory distress due to pulmonary oedema who has a combination of bandemia (left shift), atypical lymphocytosis with possible lymphoblasts, hemoconcentration, thrombocytopenia is highly suspect for infection with Sin Nombre virus (North America) or Andes virus (South America) if he recently visited a transmission area.

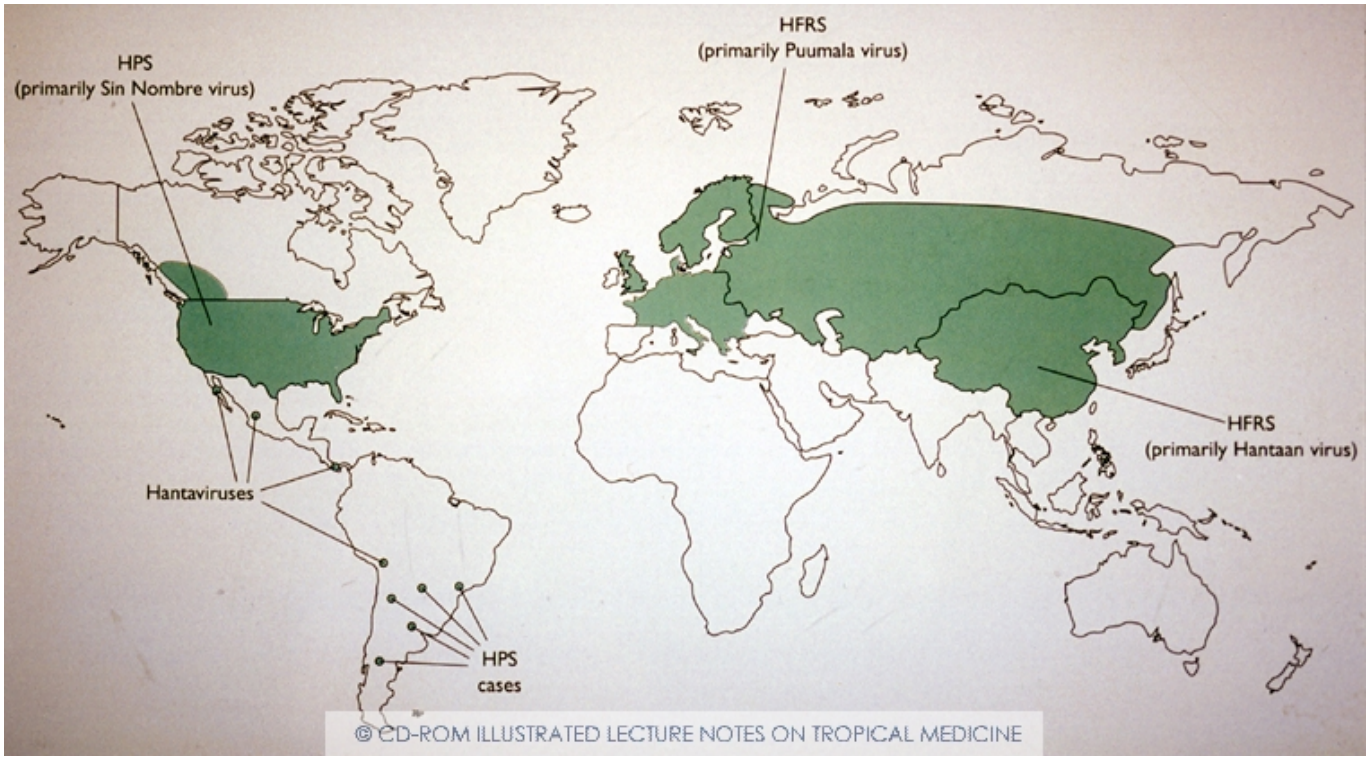
General

Hantaviruses belong to the Bunyaviridae family. They are spread by rodents and rarely by insectivores. There are several viruses named for instance, Hantaan, Dobrava, Seoul, Puumala, Andes and Sin Nombre.

Transmission

The viruses are transmitted to man mainly via the inhalation of infected particles and more rarely via ingestion of **food contaminated** with urine, saliva or faeces of rodents. Once infected, these animals excrete the virus for a long time. In the case of some of the South American viruses, it is thought that occasionally they can be transmitted from human to human. There is a close connection between the specific virus and the rodent species that forms the reservoir.

Geographical distribution



Map Hantaviruses. Copyright ITM

Infections occur worldwide, however each serotype has its own geographical range. During the Korean war, approximately 3000 UN soldiers were infected with Hantaan virus which is very virulent, producing Korean Hemorrhagic Fever. The virus derives its name from a river in Korea.

In 1993, a previously unknown serotype emerged in the USA. The virus responsible was initially called the Four Corners virus, then Muerto Canyon, and finally the name Sin Nombre was adopted. Pulmonary Hantavirus syndrome is also seen in South America.

Hantavirus infection also occurs in Belgium (especially Wallonia) and the Netherlands, as so-called epidemic nephropathy. At first the disease was called “muroid virus nephropathy”, assuming that rats or mice were involved but this nomenclature has now been abandoned.

A serious form with renal involvement, caused by the Dobrava serotype occurs in the Balkans (in Bosnia, among others).

A mild form, caused by the Puumala serotype, occurs in Scandinavia. A large outbreak of nephropathia epidemica occurred in North Sweden in 2007.

Infections with Seoul virus occur worldwide because the normal host (rat) is distributed worldwide.

Clinical aspects

Depending on the hantavirus serotype and the host, the course of the disease varies from benign to lethal. In humans the incubation period is approximately 1 to 6 weeks. Initially, there is an acute non-specific flu-like syndrome with fever, headache, asthenia, muscle pain, abdominal pain, sometimes some discomfort in the eyes with blurred vision and red conjunctivae. The benign form (Puumala) has a low mortality rate (0-0.2%) and the serious form a high mortality rate (up to 40% in the case of Sin Nombre).

In Puumala and Dobrova virus infection lumbar pain and oliguria can be expected about 4-10 days after onset. The urine contains protein and blood and interstitial nephritis is present. The creatinine and urea levels increase. In severe forms, kidney failure can be fatal, but if the patient survives, after a polyuric phase, kidney function returns to normal within two to six weeks. In approximately three quarters of cases, thrombocytopenia is present. The leukocyte count is either normal or raised. Haemorrhages can occur.

The Sin Nombre virus often leads to hantavirus pulmonary syndrome with development of tachycardia, hypotension or shock and acute pulmonary oedema with tachypnoea. The fulminant pulmonary oedema is initially non-cardiogenic and is based on a capillary leakage syndrome. Most deaths are caused by myocardial dysfunction (cardiogenic shock) and hypoperfusion rather than hypoxia. This led to the use of the term “hantavirus cardiopulmonary syndrome” (HCPS) rather than the name “hantavirus pulmonary syndrome”.

Note. Infection with Junin, Machupo, Sabia and Guanarito virus, which are New World arenaviruses transmitted through rodents, produce similar clinical syndromes with haemorrhagic tendency and sometimes neurological signs: absence of tendon reflexes, tremor, ataxia, confusion, delirium and convulsions can occur.

Diagnosis

The combination of thrombocytopenia, leucocytosis (often with left shift), elevated haematocrit, and presence of immunoblasts in peripheral blood smear is a sensitive and specific early clue to the diagnosis of pulmonary Hantavirus syndrome. These findings in a patient with rapid onset of respiratory insufficiency should suggest the diagnosis.

The diagnosis is confirmed via serology (seroconversion, IgM), RT-PCR and immunohistochemistry. The latter can be carried out on tissue biopsies, which are stored in formalin. Viral RNA can be detected via reverse transcriptase PCR. Due to the extreme sensitivity of this technique, laboratory contamination is a considerable problem. Virus culture is possible but is rarely performed.

The differential diagnosis of pulmonary Hantavirus syndrome encompasses septic shock, leptospirosis, meningococcal septicaemia, plague, tularaemia, severe influenza, SARS, myocardial infarction and fulminant pneumonia due to other causes.

The diagnosis of the other hantaviral infections will be laboratory based. Patients with acute renal failure and interstitial nephritis with or without haemorrhagic symptoms will be tested.

Treatment

In the acute phase, it is necessary to treat severe cases in an intensive care unit. Ribavirin may have in vitro activity against some viral strains but showed no benefit against Sin Nombre virus in a clinical study. Symptomatic treatment and supportive measures are essential (haemodialysis, treatment of pulmonary oedema, extra-corporeal membrane oxygenation). A great deal of attention goes to proper oxygenation, fluid balance and blood pressure control. Mechanical ventilation, extra oxygen, IV fluid and inotropic drugs should be used when needed.

Isolation of the patient is not needed.

Prevention

There is still no vaccine for most Hantaviruses. Hantavax® is a vaccine which can be used in the Far East against Seoul and Hantaan virus. Booster injections are necessary. This vaccine is not available in Europe.

Contact with rodents and their excretion products must be avoided. Places where there have been rats are best decontaminated with bleach and ventilated (do not brush away the dry dust: airborne particles!). Attracting rodents must be avoided by careful monitoring of potential food sources and hiding places. Rodent control: see further.

Rodents

Medical significance

Most medically significant rodents belong to the Muridae and the Cricetidae. Rodents play a part in many diseases, such as plague, transmitted by the rat flea *Xenopsylla cheopis* and Weil's disease, a severe form of leptospirosis transmitted via infected rat urine. Rodents play a part in conditions such as echinococcosis (*E. multilocularis*), trichinellosis, Lyme borreliosis, recurrent fever (*Borrelia recurrentis*), salmonellosis, rat bite fever, tularemia, lymphocytic choriomeningitis, *Hymenolepis diminuta* and rickettsioses such as RMSF, scrub typhus and murine typhus. Haemorrhagic fevers that are transmitted by rodents ("rodent-borne") include Hantaviruses and Arenaviruses such as Junin, Machupo and Lassa fever. Infection with *Talaromyces marneffei* is essentially a disease of rodents but can occur in AIDS patients in Southeast Asia. In 2003 an imported and infected Gambian giant rat spread monkeypox virus in the USA, a country where there had been no cases until that moment.

Importance in research

Numerous laboratories use mice and rats as experimental animals, to gain knowledge which would otherwise be impossible or very difficult to obtain. Today, working with experimental animals is avoided as much as possible, but alternative in vitro experiments are not always available. Rodent strains have been bred to provide experimental models for, e.g. immune deficiency, increased likelihood of forming tumours or hypertension, etc. These strains are maintained by inbreeding.

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