Hantavirus infection

This is a notifiable disease in the UK. See the **Notifiable diseases** article for more detail.

Hantavirus diseases are acute viral diseases in which the vascular endothelium is damaged, leading to increased vascular permeability, hypotension, haemorrhagic manifestations and shock. Hantaviruses cause two main syndromes: Hantavirus pulmonary syndrome (HPS) and haemorrhagic fever with renal syndrome (HFRS). These differ significantly in geographical distribution and in severity[1] :

- HPS is a severe flu-like illness followed by acute pulmonary inflammation leading to respiratory failure caused by acute non-cardiogenic pulmonary oedema. It has a mortality rate of about 40-50%. It is found only in the New World.
- HFRS causes a flu-like illness followed by hypotension, vascular leakage and acute kidney injury. The condition has a slower course than HPS. Mortality varies between pathogens and is 1-15%. It is only found in the Old World. It includes several diseases that formerly had other names, including Korean haemorrhagic fever and epidemic haemorrhagic fever. 'Nephropathia epidemica' is sometimes still used for a mild form of HFRS caused by Puumala virus (PUUV) or Saaremaa virus (SAAV).

The primary route of infection for both illnesses is the inhalation of live virus present in the aerosolised excreta of infected rodents.

Hantavirus human pathogens

- Over a dozen variations of Hantavirus have been discovered.

- They are found all over the world, each associated with a specific rodent reservoir [1] .
- The New World hantaviruses include sin nombre virus (SNV) and Andes virus (ANDV). The Laguna Negra, Rio Mamore, Oran, Lechiguanas and Pergamino viruses are considered variants of ANDV. The New York virus and Monongahela virus are variants of SNV. All cause HPS.
- European viruses include PUUV (which is the most common in Europe and carried by the bank vole) and Dobrava-Belgrade virus (DOBV) and SAAV (carried by particular mice). These viruses all cause HFRS.
- The main East Asian viruses are Seoul virus (SEOV) and Hantaan virus. Both cause HFRS.
- Each virus is specific to a particular rodent species.
- Public Health England (PHE) data suggest the presence of a variant of PUUV in rodent populations in the UK [2] .

Epidemiology

Hantaviruses exist throughout most of the world and are carried by various species of rodents [1] . Worldwide there are over 200,000 cases a year - at one point more than 100,000 a year occurred in China alone, although numbers there have declined dramatically [3] . In Europe most HFRS cases are registered in Russia, Finland and Sweden [4] .

HFRS

Most HFRS patients are males aged 20-50 years. HFRS patients mostly live in rural areas where the rodent hosts are populous. The only Hantavirus that causes diseases in urban areas is SEOV because its host is in domestic rats (*Rattus norvegicus* and *Rattus rattus*).

- Steep increases in Hantavirus infections in Southern Germany, with nearly 1,000 cases in the winter of 2011/12, related to an increase in the population of the bank vole [5] [6] .
- The most common Hantavirus in Europe is PUUV carried by the bank vole. Another two important, ones are DOBV and SAAV. DOBV has a high fatality rate, whilst PUUV and SAAV cause more mild disease.

- In Scandinavia and Northern Europe, a milder form of HFRS is prevalent, termed nephropathia epidemica.
- East Asian hantaviruses include Hantaan virus (HTNV), which causes severe HFRS, and SEOV. SEOV can be found worldwide and has been associated with a few cases of HFRS in the USA.
- Although HFRS was highly epidemic in China during the 1980s and 1990s, the incidence has dramatically declined during a period of eight years, as a result of comprehensive preventative measures and improved living conditions. Associated mortality rates also decreased dramatically. However, it has remained one of the top nine communicable diseases in China [3] [7] .

HPS

Although HPS is found throughout the USA, most cases are registered in the West and are caused by SNV, the predominantly found viral species.

- HPS has been reported in many countries in South and Central America, including Argentina, Brazil, Chili, Bolivia, Paraguay, Uruguay and Panama.
- HPS outbreaks in North America have been associated with increased population of host deer mouse.

Other hantaviruses

Some hantaviruses have yet been not been linked to human disease, either because they are not pathogenic for humans or because their rodent hosts are unlikely to pass them to humans [8] .

- Although clinical cases have not been reported from Africa or the Middle East, antibodies to hantaviruses have been reported among humans in both regions, and a Hantavirus was recently discovered in the African wood mouse (*Hylomyscus simus*) [8] .
- There is currently no evidence for Hantavirus-associated disease in Australia. However, it is likely that hantaviruses are carried in some Australian rodents or insectivores [8] .

Risk factors

Human infection usually occurs from inhalation of virus in aerosol from the urine, faeces or saliva of infected rodents. Other means include direct transmission via the fingers to mucous membranes, and eating contaminated food or bites; however, all of these are relatively rare.

- The Andes variation has been spread by human-to-human contact.
- Dry sweeping or vacuum cleaning areas of infected rodent droppings is a high risk, as particles are put into the air.
- Construction, utility and pest control workers entering dirty vacant buildings are at particular risk.

Hantavirus in the UK [9]

In the UK Hantavirus is rare but not unknown. PHE has been monitoring the risk of Hantavirus in the UK for some years. It concluded that seroprevalence is higher than previously thought. In other words, Hantavirus is already here but may generally cause a mild form HFRS which is largely passing 'beneath the radar' [2] . Its study concluded that:

- Hantaviruses are widely spread amongst rodents in the UK.
- Over 30% of pet rat owners have antibodies against hantaviruses.
- Most human infections in the UK are likely to be mild and nonspecific.
- Amongst occupationally exposed people like farmers, sewage and waste disposal workers, veterinarians and pest control, forestry and nature conservation workers, seropositivity is 1-3% (similar to the general public).
- When cases are diagnosed, animals in the surrounding environment test positive.
- In recent years a few pet rat-acquired cases of SEOV have had to be hospitalised in North Wales, Yorkshire, Humberside and Scotland.
- Studies of rodents trapped in Cheshire, showed the existence of a novel Hantavirus, which is related to PUUV and Tula virus (TULV).

Pathogenesis

Hantavirus is named after the Hantaan River in Korea. Hantaviruses are Bunyaviruses usually classified with the viral haemorrhagic fevers (VHFs[4]
.

- Hantaviruses infect endothelial cells.
- In HFRS the cells of the kidney are infected.
- In HCPS the pulmonary microvasculature and the cells of the spleen and lymph nodes are infected, causing a massive, pulmonary-specific immune response. The damage to pulmonary endothelium increases capillary permeability and leads to fulminant pulmonary oedema.
- Common symptomatology is due to increased vascular permeability and immune activation.

Presentation[1] [3]

Hantavirus pulmonary syndrome (HPS) - also called hantavirus cardiopulmonary syndrome (HCPS)

- Incubation period is two or three weeks, although it may be up to four weeks.
- Prodromal phase involves fever, chills and myalgia lasting 3-5 days.
- The cardiopulmonary phase is characterised by rapid deterioration over 24 hours.
- There is cardiopulmonary failure with pulmonary oedema. Patients develop dyspnoea, non-productive cough, and circulatory collapse. This stage lasts only 24-48 hours. 75% of patients with pulmonary oedema require mechanical ventilation.
- Oliguric renal failure is uncommon. When it does occur, it is due to acute tubular necrosis, as compared to the renal tubular cell damage observed in HFRS.
- Those who recover may do so rapidly. Resolution of the cardiopulmonary stage of HPS is heralded by the onset of the significant diuresis.

- After this occurs, the patient improves quite rapidly (ie convalescent phase). The chronic sequelae of HPS are minimal.
- Early diagnosis is difficult, as symptoms resemble many other viral infections.

Haemorrhagic fever with renal syndrome (HFRS)

- Incubation period is two or three weeks.
- The clinical features are of fever, haemorrhage, and renal insufficiency.
- The incubation period is 12-16 days but may be up to 42 days.
- Subclinical infections are common, especially in children.
- The disease has five stages: febrile, hypotensive, oliguric, diuretic and convalescent. Not all patients experience every stage.
- The febrile stage occurs in all patients and lasts 3-7 days, with abrupt onset of fever, temperature in the range of 40°C, headache, chills, abdominal pain, malaise, blurred vision, and lower back pain. Flushing may be observed. Petechiae may occur in the axilla and the soft palate. Subconjunctival haemorrhage is present in one third. Bradycardia may be noted. There is thrombocytopenia, which relates to prognosis and severity of renal failure. Proteinuria and microhaematuria appear.
- The hypotensive stage occurs in about 10% and lasts a few hours to two days. There is low blood pressure, and tachycardia. Patients may have acute abdomen due to paralytic ileus. In the most severe cases, after a period of a few hours to two days, haemorrhages appear. Disseminated intravascular coagulopathy, shock and multiorgan failure can occur. Neurological features can include meningoencephalitis, encephalomyelitis, seizures and Guillain-Barré syndrome. Cardiogenic shock, perimyocarditis and pulmonary oedema may also develop.
- The oliguric stage is due to acute kidney injury, which can merit dialysis. It occurs in 65% and lasts about 3-6 days. There is oliguria, hypertension, bleeding tendency, uraemia and oedema. Urea and serum creatinine rise. Patients may develop pulmonary oedema.

- The diuretic stage lasts 2-3 weeks. Diuresis of 3-6 L daily. Dehydration and shock can occur during this stage.
- The convalescent stage lasts for 3-6 months.
- Recovery usually begins in the middle of the second week. The concentrating capacity of the renal tubules recovers over many months.
- Patients may still have lack of stamina and complain often of muscular pain. Some may have an intention tremor.

- Secondary infection is common.
- Full recovery of renal function is usual.

Diagnosis

Diagnosis is based on typical clinical findings and patient history of likely rodent exposure. It is usually only made in the later stages due to non-specificity of initial symptoms.

Investigations

Hantavirus cardiopulmonary syndrome (HCPS)

- In the early stages there may be a normal FBC or slight thrombocytopenia. WCC does not rise until later in the disease. An elevated haematocrit means haemoconcentration and is an ominous sign.
- A falling platelet count is highly indicative of the cardiopulmonary phase beginning.
- LFTs: AST and LDH are often raised.
- Confirmation of diagnosis is by serological testing (eg, for virus-specific IgM) and/or RT-PCR.
- CXR may show evidence of pulmonary oedema from the outset but it usually develops over the next few days. Kerley B lines are common. Pleural effusion is seen in the late phase. The heart size is normal.

- ECG helps rule out myocardial infarction. Sinus tachycardia is common. Death usually occurs with pulseless electrical activity (electro-mechanical dissociation).

Haemorrhagic fever with renal syndrome (HFRS)

This particularly shows abnormalities of the renal system, although any of the above may also occur.

- Albuminuria can be heavy.
- The rise in creatinine will depend upon the severity of the disease.
- Thrombocytopenia relates to prognosis.
- Falling haematocrit, coagulopathy, falling fibrinogen, and electrolyte imbalances may all be present.
- Confirmation of diagnosis is by serological testing (eg, for virus-specific IgM) and/or RT-PCR.

Management

- Treatment is mainly supportive cardiovascular, respiratory and renal function support, with fluid and electrolyte homeostasis. Inotropic support may be required to maintain mean arterial pressure above 70 mm Hg [10] .
- The antiviral ribavarin is not beneficial, although antibiotics may be required for secondary infection [11] .
- In HPS, intubation and respiratory support may be required. The use of extracorporeal membrane oxygenation (ECMO) in decompensated patients has also been shown to be beneficial. ECMO supports the failing heart and lungs long enough to allow recovery [12] .

Prognosis

- HPS has a mortality of 40-50%.
- HFRS is most often less severe but can also be catastrophic. However, Dobrova and Hantaan viruses have a mortality rate of up to 15% [13] .
- Most deaths occur within 24 hours of hospital admission.

- The global scale of Hantavirus mortality remains highly significant. In China, more than 1.5 million cases of HFRS, resulting in more than 46,000 deaths (around 3.4%), were reported between 1950 and 2007 [3] [14] .
- Symptomatic recovery is usually complete, although some survivors have reported persisting myalgia, weight gain and persisting tiredness [15] . Some studies suggest that survivors of HPS have persisting renal sequelae, including chronic kidney disease [14] .

Prevention

Hantavirus is a zoonosis. Contact with infected rodents or their excreta is the means of spread.

- Hantaviruses are stable in air and can survive >10 days at room temperature and >18 days at 4°C and -20°C
- The virus can easily be killed by fat solvents (alcohol), detergents, disinfectants and bleach. Thus, wetting before cleaning (using gloves) is effective.
- The risk of infection is very low for most travellers. Travellers may be at risk in any environment where rodents are present in large numbers. Adventure travellers, backpackers, campers and travellers with occupational exposure to rodents in countries or areas at risk for hantaviruses should take precautions to exclude rodents from tents or other accommodation and to protect all food from rodent contamination.
- Based on current human population growth and development trends, Hantavirus diseases are likely to become more common unless public health measures are taken to reduce rodent numbers in human communities [16] .

Vaccines [17]

- Despite ongoing research, no World Health Organization-approved vaccine has gained widespread acceptance. However, two HFRS vaccines are in use in the Far East.

- Approximately two million doses of inactivated rodent brain- or cell culture-derived HFRS vaccines are given annually in China [3] . This vaccination, along with public education and rodent control measures, has coincided with a reduction in HFRS cases to less than 20,000 per year, However, China still has the highest number of HFRS cases and deaths in the world [3] .
- A rodent brain-derived inactivated HFRS vaccine has also been used in the Republic of Korea since the early 1990s and has similarly corresponded with reduced numbers of HFRS cases, although the conferred immunity may be relatively short-lasting [18] [19] .
- There are no HFRS vaccines approved for use in Europe. Even if the Chinese or Korean vaccines met European regulatory standards, animal studies suggest that vaccines derived from HTNV or SEOV would not protect against PUUV [17] .

History of Hantavirus

- Hantavirus is one of the older VHFs.
- A disease resembling HFRS was mentioned in a Chinese text from 960 AD.
- English sweating sickness, a mysterious illness that struck England in the 15th century, is consistent with a Hantavirus infection. There were five major epidemics between 1485 and 1551. Outbreaks occurred during summer months, preceded by harsh winters and periods of prolonged rainfall. This is consistent with current observations of Hantavirus epidemics. SEOV and its vector, the black rat (*Rattus rattus*), a common rodent in Europe, could have been the culprit.
- Hantavirus disease was also suggested to be the cause agent of many cases of epidemic nephritis during the American Civil War and World War I.
- During World War II outbreaks of nephritis among German troops on the Eastern front and in Finland, where hantaviruses are endemic, were classified as rodent-borne.
- During the Korean War (1951-1976), 3,000 soldiers developed a disease characterised by fever and renal failure, with a fatality rate of 10% [20] .

- In 1993 a Hantavirus named Muerto Canyon virus - later changed to sin nombre virus (SNV) - and its rodent reservoir (the deer mouse *Paromyscus maniculatus*) were identified. This was six months after an outbreak of unexplained pulmonary illness in the Southern USA (Arizona, New Mexico, Colorado and Utah).
- Retrospective serological investigations on unexplained pulmonary deaths put the earliest proven case in 1959, although the condition is recognised in older Navajo Indian medical traditions as being associated with mice.

Dr Mary Lowth is an author or the original author of this leaflet.

Further reading

- Hantavirus; Centers for Disease Control and Prevention

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