Emerging infections: haemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome

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Abstract

Hantaviruses form a genus within the Bunyaviridae family and have a world-wide distribution. These negative stranded RNA viruses may be the cause of two different types of disease in humans: Haemorrhagic Fever with Renal Syndrome (HFRS) in Eurasia and Hantavirus (Cardio) Pulmonary Syndrome (HCPS), the latter seen mainly in North and South America. Here we will discuss important aspects of hantavirus disease focussing on epidemiology, clinical manifestations and (experimental) treatment. This comprehensive overview may serve as an introduction and reference article for clinicians and scientists new in the emerging field of hantavirus diagnosis and research.

Introduction

Pathogenic hantaviruses, which are all carried by chronically infected reservoir rodents, may be the cause of two types of disease in humans after inhalation of aerosolized rodent excreta (1). In North and South America hantaviruses cause Hantavirus (Cardio)Pulmonary Syndrome (HCPS), a syndrome for which the causative hantavirus was first isolated in 1993 in the four corners region in the USA (2). Many of the emerging characteristics of hantavirus caused HCPS were present in the 2012 outbreak of HCPS in Yosemite Park, USA and confirmed the constant threat of New World hantavirus outbreaks (3). HCPS epidemiology is characterized by small, clustered outbreaks that are clearly associated with risk factors linked to rodent exposure (4). Reported case fatality rates go up to 60% often related to respiratory failure and hypoxia (5). The second syndrome associated with hantavirus infections is caused by pathogenic hantaviruses circulating in Europe and Asia. Viruses like Hantaan and Dobrava are able to cause Haemorrhagic Fever and Renal Syndrome (HFRS) (6). HFRS has a more endemic character, compared to HCPS, especially in Northern Europe, Eastern Europe and South-East Asia. First reports of the classic HFRS syndrome, a combination of renal failure and haemorrhage accompanied by high fever, come from early 1900s in Russia, while also infections of soldiers in World War I and II have been suggested to be actually caused by hantavirus infections. The first pathogenic hantavirus, the Hantaan virus, was isolated in 1976 close to the Hantaan river in Korea from a striped field mouse (*Apodemus agrarius)* (7). Reservoir rodents only experience subclinical infection and show no signs or symptoms comparable to those seen in infected humans. The very specific characteristics of hantavirus transmission and incidence all directly linked to rodent exposure and rodent population dynamics make hantavirus disease an interesting public health challenge but in theory preventable infections. However, recent studies clearly show unawareness under clinicians as a potential factor contributing to the continuous emergence of hantavirus disease.

Virology

Hantaviruses are small, negative stranded, enveloped viruses with an RNA genome consisting of three segments: the large-segment codes for the RNA-polymerase, the medium-segment for envelope surface glycoproteins and the small-segment codes for the nucleocapsid protein. The termini of these RNA segments contain conserved regions that are suitable for molecular detection of hantaviruses in patients and reservoir hosts. Until now more than 70 hantavirus species have been identified in rodents, insectivores and recently in bats. Around 30 of these hantavirus species are associated with disease in humans and all of these are rodent-borne hantaviruses. In general each hantavirus is associated with one reservoir host species which for the most prevalent hantavirus species are: *Myodes glareoulus* (Puumala), *Apodemus agrarius* eastern subtype (Hantaan), and for Seoul the *Rattus rattus* and *Rattus norvegicus*. This knowledge can be of importance for clinicians and public health workers since data on rodent species populations provides insight in the potential hantaviruses circulating in a defined area.

Haemorrhagic fever and renal syndrome

In Eurasia, in (hantavirus) literature often referred to as the Old World, the most prevalent hantaviruses are Puumala, Dobrava, Seoul and Hantaan. Patients infected with one of these Old World hantaviruses classically present with the triad of fever, renal failure potentially complicated by haemorrhage (8). The combination of these hantavirus associated symptoms, is known as Haemorrhagic Fever with Renal Syndrome (HFRS). In general patients infected with Puumala hantavirus show a milder form of HFRS which is often called 'Neprhopathia epidemica'. After an incubation period varying between two to three weeks 100% of the symptomatic HFRS patients develop fever. After this febrile phase increased vascular permeability and an inadequate vascular tone could lead to hypotension and pulmonary oedema which may eventually lead to shock. Renal failure in HFRS often develops in a late acute stage (9,10) and patients typically develop oliguria, which is followed by a diuretic phase. Kidney biopsies show a damaged medulla, interstitial oedema and haemorrhage, together with cytotoxic T-cell infiltrates and the extravasation of erythrocytes (11). Laboratory analysis shows clear thrombocytopenia, increased creatinine levels, an elevated, left-shifted, serum leukocyte count and an elevated C-reactive protein (CRP) at a level approaching those in certain bacterial infections. HFRS is a widespread zoonotic disease with endemic areas spreading from the cold wintry climate in Northern Europe up to the subtropical areas in South-East Asia.

Hantavirus cardiopulmonary syndrome

In the New World (North and South America), hantaviruses like Andes virus and Sin Nombre virus are able to cause Hantavirus (cardio)Pulmonary Syndrome (HCPS). HCPS, unlike HFRS, mainly affects the lungs and heart of infected individuals (12). Acute respiratory distress can develop very rapidly after symptoms of fever, myalgia, and non-specific upper respiratory tract manifestations. HCPS is especially characterized by (pulmonary) oedema as a result of endothelial dysfunction eventually leading to respiratory distress which is the main cause of death in HCPS patients. The respiratory distress leads to hypoxia, cardiac insufficiency with very high intubation rates and need for use of inotropics (13,14). Case fatality rates vary from 30-60% (13-16). Patients show a drastic increase in the change of survival when

they receive extracorporeal membrane oxygenation which indicates reversible damage in the acute phase of the disease (17).

Hantavirus disease

For adequate recognition of acute hantavirus infection knowledge of possible non-specific presentations is important. Recent papers debate the absolute difference between HFRS and HCPS hantavirus syndromes. It actually seems that symptoms overlap to a large extent. HFRS cases could present with acute respiratory failure without signs of kidney involvement, while HCPS patients may show renal complications (18). Therefore using the term 'hantavirus disease' for all hantavirus related syndromes described may be more appropriate.

Diagnosis

Although the extent of viraemia largely varies between hantavirus related syndromes, in many cases the viraemic stage is short and diagnosis is usually requested after this period. The time period in which hantavirus can be detected by PCR usually coincides with the virulence of the virus involved. The time period in which Puumala hantavirus - the causative agent of a relatively mild form of haemorrhagic fever and renal syndrome - can be detected, is up to four days after onset of disease symptoms. In contrast the 'Old World' hantaviruses Hantaan or Seoul viruses that generally cause more serious disease, may be detectable until 8-10 days after onset. Practically the diagnosis of hantavirus infection in many cases relies on the demonstration of hantavirus specific IgM and/or IgG serum antibodies by Enzyme-Linked Immuno Sorbent Assay (ELISA) or an Immunofluorescence assay (IFA). Almost all patients with acute hantavirus-related disease form ELISA or IFA detectable serum IgM and IgG antibodies against the nucleocapsid protein of the virus, detectable upon presentation. It is important to realize that a high level of cross reactivity exists between the hantaviruses of Serotype 1 "Dobrava-Belgrade virus, Saaremaa virus, Seoul virus and Hantaan virus" and between those of Serotype 2 "Puumala virus, Tula virus, Topografov virus and Sin-Nombre-like viruses".

Treatment

Since effective antiviral treatment for hantavirus disease is lacking, the initiation of prompt and proper symptomatic and supportive treatment for HFRS and HCPS is crucial. This includes monitoring of fluid balance, diuresis, kidney function and the use of fresh frozen plasma/transfusions in case of haemorrhagic complications when necessary for HFRS. In HCPS oxygenation is of major importance, and as mentioned before, ECMO may drastically increase survival in New World hantavirus infections. Small trials and case reports have shown that ribavirin treatment may be useful in the very early phase of HFRS by reducing the risk of haemorrhagic events and the severity of renal insufficiency. Larger trials are needed to corroborate these findings. In contrast two clinical trials only showed adverse effects of ribavirin treatment in HCPS. (19;20). Both interferon and adjunctive prednisolone treatment have not showed beneficial effects in placebo-controlled clinical trials. Recently, two case reports described efficient treatment of severe PUUV infected patients in Finland with the bradykinin receptor antagonist icatibant (21).

Concluding remarks

Since adequate treatment and an effective vaccine are lacking for hantavirus disease raising awareness and increasing knowledge on the epidemiology and pathophysiology of hantavirus infections are essential. In addition, currently practical measures leading to rodent control and reduction of numbers of infected rodents seem to be the best way to reduce the burden of hantavirus disease in humans (22,23).

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