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Review

Haemorrhagic fever with renal syndrome: literature review and distribution analysis in China

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SUMMARY

Hantaviruses infect their reservoir hosts and humans, but the infection only causes disease in humans. In Asia and Europe (the Old World), the hantaviruses usually cause haemorrhagic fever with renal syndrome (HFRS). This article summarizes the current understanding of hantavirus epidemiology, as well as the clinical manifestations, pathogenesis, renal pathology, diagnosis, treatment, and prevention of HFRS. Moreover, the spatiotemporal distribution of HFRS was analysed based on the latest data obtained from the Chinese Centre for Disease Control and Prevention, for the period January 2004 to April 2015, to provide valuable information for the practical application of more effective HFRS control and prevention strategies in China.

1. Introduction

Haemorrhagic fever with renal syndrome (HFRS), a rodent-borne infectious disease caused by hantaviruses, is clinically characterized in humans by fever, haemorrhage, headache, abdominal pain, and acute kidney damage. HFRS occurs primarily in the Old World and is endemic all over China, with the exception of the Taiwan region.[1,2] China has the highest incidence of HFRS, accounting for approximately 90% of HFRS cases globally in the last few decades. During recent decades, the incidence of HFRS has fluctuated, but it has remained one of the top nine communicable diseases in mainland China. This study was performed to review what is known about HFRS and to identify its epidemiological distribution in China.

2. HFRS-associated hantavirus infection

Hantaviruses are single-stranded, enveloped RNA viruses of the *Bunyaviridae* family. They cause two human syndromes, hantavirus cardiopulmonary syndrome (HCPS) in the Americas and HFRS in Europe and Asia.[3] Seven sero/genotypes of HFRS-associated hantaviruses have been identified (Hantaan, Dobrava, Saaremaa, Seoul, Amur, Puumala, and Far East), and two of these, Hantaan virus (HTNV) and Seoul virus (SEOV), are the major causative agents of HFRS in China.[4]

Hantaviruses are unexpectedly stable in air and can survive >10 days at room temperature and >18 days at 4 °C and −20 °C.[5,6] Hantaviruses are mainly carried by rodents, insectivores, and bats. They are transmitted to humans via inhalation of virus-contaminated aerosols of excreta and secreta, via contaminated food, and rarely, via rodent bites.[7] Hantavirus infection has also been reported in several species of domestic animals, such as cats, dogs, pigs, and rabbits.[8] The survival of hantaviruses depends on the maintenance of persistent infection within their reservoir hosts.[9] Thus, hantavirus emergence in humans depends on the following factors: (1) the external environmental factors including temperature, rainfall, relative humidity, land use, the normalized difference vegetation index (NDVI), the temperature vegetation dryness index (TVDI), and elevation, which play significant roles in reservoir host density and the level of exposure to infectious viruses;[1,10,11] (2) the frequency of contact between the human and rodent populations, which is associated with human activities, living conditions, working conditions, and urbanization;[12] and (3) the proportion of infections resulting in HFRS, which may be due to the susceptibility of humans to hantaviruses and may be influenced by population immunity and vaccination.[3,13]

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3. Clinical manifestation of HFRS

The clinical picture of HFRS is characterized by acute renal failure, accompanied by haemorrhage and flu-like symptoms, such as fever, headache, and abdominal/back/orbit pain.[14] Kidney manifestations are characterized predominantly by massive proteinuria, haematuria, and a rapid decline in glomerular filtration rate (GFR), resulting in oedema, disorder of electrolytes and acid–base balance, and the need for dialysis.[15] Severe complications may involve multiple systems. In the neurological system, meningoencephalitis, acute disseminated encephalomyelitis, generalized seizures, Guillain–Barré syndrome, urinary bladder paralysis, and seizures have been reported. In the cardiopulmonary system, shock, perimyocarditis, and pulmonary oedema may develop. Disseminated intravascular coagulopathy, multiple bleedings, pancreatitis, and multiorgan failure have also been observed, all of which may lead to a lethal outcome.[16]

Classic clinical HFRS occurs in five phases: febrile phase (3–7 days), hypotensive phase (hours to 2 days), oliguric phase (3–7 days), diuretic phase (polyuria) (days to weeks), and convalescent phase (2–3 months). Long-term outcomes after HFRS show a much higher prevalence of renal tubular dysfunction, glomerular hyperfiltration, chronic glomerulonephritis, hypertension, acute myocardial infarction, and stroke compared with the general population.[16–18]

4. Pathogenesis of HFRS

Humans are not a natural reservoir and, therefore, become infected when they come into contact with the excreta of reservoir hosts, such as rodents. Infections can result in serial diseases, and the pathogenesis and outcomes vary with the different species of hantavirus. The hallmarks of HFRS are increased vascular permeability, thrombocytopenia, coagulopathy, and haemorrhagic manifestations. The molecular mechanisms of HFRS are not well understood. A complex interplay between hantaviruses, host immune responses, and endothelial cells has emerged as a common theme. Hantavirus infection directly or indirectly leads to the activation of signalling pathways and the dysregulation of immune cells, such as CD4+ T-cells and CD8+ T-cells. The inflammatory response leads to the activation of the complement system, the formation of circulating immune complexes, and the secretion of multiple proinflammatory cytokines. These cytokines promote endothelial cell dysfunction and capillary leakage.[14,19] Haemorrhage is common in HFRS. The coagulopathy appears to be a thrombosis–fibrinolysis imbalance combined with platelet deposition and dysfunction. Severe thrombocytopenia is associated with a more severe course of the disease in HFRS.[20,21]

5. Renal pathology of HFRS

Increased vascular permeability in HFRS is indicated by widespread capillary engorgement, focal haemorrhage, and interstitial oedema in the renal medulla. Hantavirus nephropathy is an uncommon aetiology of acute renal failure due to hantavirus infection. Light microscopy of renal biopsies from hantavirus nephropathy patients shows interstitial haemorrhage and oedema, acute tubular necrosis, inflammation of the renal microvessels, cortical peritubular capillaritis, and medullary vasa recta inflammation, with minor changes in the glomeruli. Immunohistochemical studies have shown the deposition of circulating immune complexes and activation of the complement system. Furthermore, anti-CD3, anti-CD68, and anti-CD34 antibodies have positively highlighted the involvement of T-cells and macrophages in renal microvascular inflammation.[22] Electron microscopy has revealed podocyte foot process effacement, which indicates that hantavirus infection might perturb podocyte integrity, resulting in glomerular proteinuria. These alterations of acute tubular necrosis and podocytes may be reversible and transient and may resolve within weeks to months.[23]

6. Diagnosis and biomarkers of HFRS

The diagnosis of hantavirus infections in humans is based on clinical and epidemiological information as well as laboratory tests. Laboratory testing should be performed for patients with fever of unknown origin, thrombocytopenia, renal failure, or respiratory distress, who live in hantavirus disease-endemic regions. The laboratory diagnosis of hantavirus infection is based mainly on three primary categories of test: serology, molecular methods, and immunochemistry (Table 1).[24–38] The most practical approach is a serological test to detect IgM/IgG antibodies of the three structural hantavirus proteins (Gn, Gc, and N) using ELISAs. Real-time RT-PCR is a sensitive tool for the early detection of hantavirus RNA that can detect hantavirus RNA prior to the appearance of IgM antibodies. Therefore, the combination of IgM/IgG ELISAs and RT-PCR is a sensitive and desirable approach for the laboratory diagnosis of hantavirus infection. Immunohistochemistry is of great utility for identifying viral antigens in tissues, particularly in fatal cases without other types of sample. Virus isolation from human samples is rare, and it is not an option in the diagnosis of human hantavirus infection.

Many new biomarkers have been reported to be associated with a severe course of hantavirus infection. Several examples that have been reported recently are listed here. CD163 is expressed by monocytes/macrophages in response to inflammatory stimuli. The level of plasma soluble CD163 in HFRS patients has been found to increase at fever onset and to peak in the oliguric phase, positively correlating with the severity and progression of disease.[39,40] The level of high mobility group box protein 1 (HMGB-1) has been found to correlate positively with the white blood cell count and blood urea nitrogen (BUN) and to correlate negatively with the platelet count, albumin, and uric acid (UA). The HMGB-1 level has been found to be predictive of the prognosis in HFRS patients.[41] The serum decoy receptor 3 (DcR3) level has been shown to be positively correlated with tumour necrosis factor alpha (TNF-α) and to peak during the oliguric phase, reflecting the severity of kidney damage, characterized by elevated BUN, creatinine, and proteinuria.[42] Interleukin 21 (IL-21) has been shown to stimulate T-cell and B-cell responses in the pathogenesis of HFRS. IL-21 begins to increase in the fever phase, peaks in the oliguric phase, and is associated with the disease severity of HFRS.[43] As one of the vascular permeability cytokines, the serum level of vascular endothelial growth factor (VEGF) has been reported to be persistently elevated throughout the various stages and types of HFRS and to be closely correlated with the progression of HFRS as well as the severity of kidney damage.[44]

7. Treatment and prevention of HFRS

The treatment of HFRS is based on the clinical symptoms of the disease and occasionally includes haemodialysis, oxygenation, and shock therapy. There is no specific therapy available. The use of ribavirin, an antiviral agent, has resulted in a reduction in morbidity and a decrease in fatalities in HFRS patients in China.[45] Other promising new ideas, including the use of a bradykinin receptor antagonist (bradykinin is involved in vasodilatation and increases vascular permeability) and passive immune therapy with human plasma, have mainly been based on similar findings in the hamster model, and have not been used widely in humans.[46,47] Steroid-based anti-inflammatory treatment options have been described in several case reports, particularly in patients with