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Treatment of hantavirus pulmonary syndrome

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Abstract

Viruses in the genus *Hantavirus* can cause one of two serious illnesses when transmitted from rodents to humans: hemorrhagic fever with renal syndrome (HFRS) or hantavirus pulmonary syndrome (HPS). Of the two diseases, HPS is more severe with an approximate 40% mortality across the Americas. The high rate of mortality could be reduced if effective therapeutics could be discovered for treatment of this illness. Herein we review approaches being explored for the discovery of therapeutics for HPS and how they could be employed in treatment and prevention of disease.

Keywords: Hantavirus; HPS; HFRS; Hantavirus pulmonary syndrome; Bunyavirus; Antiviral therapy; Ribavirin

1. Introduction

Hantaviruses cause two types of serious illness when transmitted from their rodent reservoirs to humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) (Lee and Johnson, 1982; Wong et al., 1988; Peters and Khan, 2002). These viruses are harbored by both Old-World and New-World rodents, and hence, their epidemiology reflects the geographical restriction imposed by the host range of the rodent vector (Plyusnin and Morzunov, 2001). Hantaviruses first came to the attention of western medicine in the early 1950s when more than 3000 US troops fighting in the Korean war became ill with Korean hemorrhagic fever, which later came to be known as HFRS (Johnson, 2004; Maes et al., 2004). The wave of HFRS cases presumably resulted from a high contact rate with rodents chronically infected with Hantaan virus (HTNV) as soldiers lived and fought in the open fields. The second category of illness, HPS, was first recognized in 1993 when an outbreak of severe respiratory disease struck in the Four Corners region of the US (Nichol et al., 1993). The hantavirus responsible for this disease, Sin Nombre virus (SNV), is harbored by the deer mouse (*Peromyscus maniculatus*).

Since the Four Corners outbreak, more than 2000 cases of HPS have occurred in sporadic fashion throughout the Americas, leading to the discovery of many different strains of these viruses and their associated rodent reservoirs (Barclay and Rubinstein, 1997; Bayard et al., 2004; Bohlman et al., 2002; Chu et al., 2006; Figueiredo et al., 2003; Fulhorst et al., 1997; Hjelle et al., 1996; Johnson et al., 1997, 1999; Levis et al., 1997; Lopez et al., 1996; Vincent et al., 2000; Williams et al., 1997). In addition to the United State and Canada, HPS cases have been confirmed in Argentina, Bolivia, Brazil, Chile, Paraguay, Panama and Uruguay. The initial Four Corners outbreak, followed by the many others throughout the Americas over the past 15 years, has elevated attention to these viruses as a global health problem.

In addition to their recognition as a global health problem, hantaviruses have been on and off the Centers for Disease Control and Prevention Category A list of potential bioterror agents, reflecting ambiguity as to the threat posed by these viruses (Bronze et al., 2002). When hantaviruses are viewed individually, rather than as a genus, it becomes obvious why certain hantaviruses pose a greater bioterror threat than others. For example, the South American Andes virus (ANDV) has continued to have a high mortality (30–50% HPS case–fatality rate) and is the only hantavirus for which there is evidence of person-to-person transmission (Wells et al., 1997). All of the HPS-causing viruses show a rapid disease course with serious pulmonary symptoms. Cases usually appear in rural areas, mandating transport of the patient to the nearest hospital. Hence,

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the clinical course of the disease, whether it occurs through an intentional act or accidental exposure, requires rapid diagnostic tests and treatment.

2. Classification, structure and replication strategy

Members of the genus *Hantavirus*, family *Bunyaviridae*, have a tri-segmented, negative-sense, single-strand RNA genome enclosed within a membrane derived from the Golgi apparatus (Schmaljohn et al., 1983; Schmaljohn and Hooper, 2001). The three gene segments, L, S, and M encode the L protein, nucleocapsid protein (N), and envelope glycoproteins (Gn and Gc; previously G1 and G2), respectively. Hantaviruses enter host endothelial cells via interaction of the larger viral glycoprotein (Gn) with the host's cell surface receptor(s); β1 and β3 integrins (Gavrilovskaya et al., 1999, 1998). Following entry, the precise steps are unknown, however, it is presumed that the virus is uncoated to liberate the three nucleocapsids that contain genomic RNA complexed with N and L proteins. Transcription, replication and assembly occur within the cytoplasm with L and S transcripts translated on free ribosomes, while the Gn/Gc precursor is co-translated on the rough endoplasmic reticulum (Schmaljohn and Hooper, 2001). For the Old-World hantaviruses, experimental evidence clearly shows that the viral envelope derives from budding into the Golgi apparatus, while New-World viruses may mature at the plasma membrane (Ravkov and Compans, 2001). The molecular determinant(s) responsible for differences in the clinical course of the two diseases are unknown.

3. Clinical syndrome

Hantaviruses cause a spectrum of vascular-leak syndromes in humans ranging from proteinuria to pulmonary edema and frank hemorrhage (Khan and Khan, 2003; Peters and Khan, 2002; Peters et al., 1999; Plyusnin et al., 2001; Schmaljohn and Hjelle, 1997). Old-World hantaviruses have been associated with a mild-to-severe disease, HFRS, that is characterized by fever, vascular leakage resulting in hemorrhagic manifestations, and renal failure (Lee, 1982; Lee and van der Groen, 1989; Vapalahti et al., 2003).

HPS, caused by New-World hantaviruses, has been associated with a much higher rate of fatal illness. The illness is characterized by fever and vascular leakage resulting in noncardiogenic pulmonary edema followed in severe cases by shock with lactic acidosis, a low cardiac index and elevated systemic vascular resistance (Enria et al., 2001). Many authors prefer the term hantavirus cardiopulmonary syndrome (HCPS) to emphasize the important role of cardiogenic shock; among hospitalized patients, death almost invariably results from cardiogenic shock rather than respiratory failure (Hallin et al., 1996; Ferrés et al., 2007; Mertz et al., 2006, 2004; Saggioro et al., 2007; Vial et al., 2006). The illness caused by SNV and related New-World viruses bears some resemblance to HFRS, except that the lungs are targeted for capillary leakage instead of the kidneys (Moolenaar et al., 1997, 1995; Zaki et al., 1995). Case–fatality ratios for HPS caused by the most prevalent North American and South American hantaviruses, SNV and ANDV, respectively, range from 30 to 50% (Doyle et al., 1998), while other strains such as the Leguna Negra (Paraguay) and Juquitaba viruses (Brazil) have a much lower mortality (∼15%).

In striking contrast to all other HPS- and HFRS-causing viruses, ANDV, found in Chile and Argentina, is associated with person-to-person transmission (Chaparro et al., 1998; Enria et al., 1996; Ferrés et al., 2007; Martinez et al., 2005; Padula et al., 1998; Vitek et al., 1996; Wells et al., 1997). In Chile, the risk of person-to-person transmission is greatest among close household contacts (sex partners and persons who sleep in the same bed or room) of index cases. In a recent prospective study of household contacts of index patients with HPS in Chile, the overall risk of secondary infection within the household was 3.4%. However, the risk was 17.6% among sex partners of index cases, versus 1.2% among other household contacts (Ferrés et al., 2007).

Among HPS cases in which a short, defined exposure in a high-risk area could be determined, the median incubation period from exposure to the onset of symptoms was 18–19 days with a range of 11–32 days for ANDV (Mertz et al., 2006; Vial et al., 2006) and 9–33 days for SNV (Young et al., 2000). The true range is certainly greater (one reported case had an incubation period of 46–51 days), but well-documented short incubation periods have not been reported. Also, in a prospective study of household contacts of index cases with HPS in Chile, ANDV RNA could be detected in peripheral blood cells by RT-PCR up to 2 weeks before the onset of symptoms or the appearance of anti-hantavirus antibodies in persons who subsequently developed HPS (Ferrés et al., 2007).

The diagnosis, clinical course and supportive care for patients with New-World hantaviral infections have recently been reviewed (Mertz et al., 2006). The clinical course can be broken into five distinct phases, with some variation in incidence and severity of symptoms among patients (Fig. 1). Following the incubation period, the patient develops a prodrome of fever, myalgia, and progressively worsening thrombocytopenia, often accompanied by headache, back pain, abdominal pain, and diar-

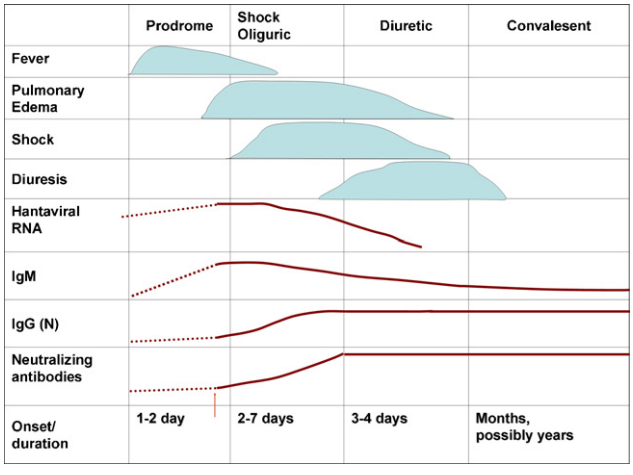

Fig. 1. Clinical course of hantavirus pulmonary syndrome.