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Review

The pathogenesis of nephropathia epidemica: New knowledge and unanswered questions

Jukka Mustonen [a,b,*], Satu Mäkelä [a,b], Tuula Outinen [b], Outi Laine [a,b], Juulia Jylhävä [a], Petteri T. Arstila [c], Mikko Hurme [a,d], Antti Vaheri [e]

[a] School of Medicine, University of Tampere, Tampere, Finland
[b] Department of Internal Medicine, Tampere University Hospital, Tampere, Finland
[c] Haartman Institute and Research Programs Unit, Immunobiology, University of Helsinki, Helsinki, Finland
[d] Pirkanmaa Hospital District (Fimlab Laboratories), Tampere, Finland
[e] Haartman Institute, Department of Virology, University of Helsinki, Helsinki, Finland

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ABSTRACT

Puumala virus (PUUV) causes an acute hemorrhagic fever with renal syndrome (HFRS), a zoonosis also called nephropathia epidemica (NE). The reservoir host of PUUV is the bank vole (*Myodes glareolus*). Herein we review the main clinical manifestations of NE, acute kidney injury, increased vascular permeability, coagulation abnormalities as well as pulmonary, cardiac, central nervous system and ocular manifestations of the disease. Several biomarkers of disease severity have recently been discovered: interleukin-6, pentraxin-3, C-reactive protein, indoleamine 2,3-dioxygenase, cell-free DNA, soluble urokinase-type plasminogen activator, GATA-3 and Mac-2 binding protein. The role of cytokines, vascular endothelial growth hormone, complement, bradykinin, cellular immune response and other mechanisms in the pathogenesis of NE as well as host genetic factors will be discussed. Finally therapeutic aspects and directions for further research will be handled.

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* Corresponding author at: School of Medicine, Lääkärinkatu 1, 33014 University of Tampere, Finland. Tel.: +358 50 3444 698.
E-mail address: jukka.mustonen@uta.fi (J. Mustonen).

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1. Introduction

Hantaviruses circulate in a variety of rodent species across Eurasia, occasionally spreading to humans to cause an illness known as hemorrhagic fever with renal syndrome (HFRS), characterized by fever, increased vascular permeability, coagulation defects and acute kidney injury (AKI) (Vaheri et al., 2013b). Severe forms of HFRS caused by Hantaan and Dobrava virus occur in the Far East and in southeastern Europe, while Puumala virus (PUUV) produces a milder disease, nephropathia epidemica (NE) in the Scandinavian countries and other areas of Northern, Eastern and Central Europe. Finland has the highest incidence of recognized cases of NE, with thousands of cases occurring annually, and the case fatality rate of up to 0.4%. No vaccine or specific therapy is available for the disease.

Research on the pathogenesis of NE has been limited by the inability of investigators to reproduce the features of the disease in laboratory animals. However, human clinical studies are now shedding light on its underlying mechanisms and suggesting specific countermeasures to reduce the severity of illness. In this paper, we review current understanding of the pathogenesis of NE and identify gaps in the knowledge that should be targets for future research. We first present basic information on hantaviruses, their rodent reservoirs and routes of transmission to humans. We then summarize the clinical features of NE and biomarkers of disease severity, review the major pathophysiologic mechanisms, focusing in particular on the role of innate and adaptive immune responses in producing vascular leakage, coagulation defects and other features of illness. In the concluding section, we discuss current therapeutic approaches, and focus on the need to develop new treatments that block or neutralize deleterious host responses to infection.

2. Hantaviruses and their reservoir hosts

Puumala virus (PUUV) is a member of the *Hantavirus* genus in the family of Bunyaviridae. Hantaviruses are enveloped viruses (diameter about 120 nm) with a single-stranded RNA genome divided in three segments. They are called L (large) encoding the RNA polymerase, M (medium) encoding the two glycoproteins Gn and Gc, and S (small) encoding the nucleocapsid protein N (Hepojoki et al., 2012). In some hantaviruses, including PUUV, a nonstructural protein NSs is found, which can function as a weak interferon inhibitor (Jääskeläinen et al., 2007) but may have other functions as well (Rönnberg et al., 2012). The reservoir host of PUUV is the bank vole (*Myodes glareolus*), which is common in Europe. Humans get infected from inhaled aerosols of bank vole excreta and secreta (urine, feces, saliva), typically in human dwellings such as woodsheds, summer cottages, barns and cowsheds (Vaheri et al., 2013a; Vapalahti et al., 2003). PUUV is quite stable and may remain infective for two weeks at room temperature (Kallio et al., 2006) and presumably for more time at colder temperatures. PUUV is not transmitted from human-to-human but probably occasionally via platelets or other blood products (Sinisalo et al., 2010). Risk factors to catch PUUV infection include forestry, farming, camping, summer cottages, heating with wood, crises, military activity, male gender and cigarette smoking (Van Loock et al., 1999; Vapalahti et al., 2010).

In the Nordic countries PUUV is the only hantavirus causing HFRS while in central and eastern Europe there are also hantaviruses carried by *Apodemus agrarius* mice (Kurkino and Saaremaa viruses), and *A. flavicollis* and *A. ponticus* mice (Dobrava and Sochi viruses) (Klempa et al., 2013). Rats carrying Seoul virus have been detected also in Europe (Heyman et al., 2011). However, PUUV is by far the most common pathogen, although Dobrava and Sochi infections have considerably higher case-fatality rates. The highest number of human PUUV infections in Europe is reported from Finland; the record was in the year 2008 when 3259 cases were diagnosed. PUUV infections are also quite common in Northern Sweden, the Ardennes regions of Belgium and Northern France, in Southwestern Germany and some parts of European Russia (Vaheri et al., 2013a). PUUV infections are widely distributed in Europe with the exception of the far north and the Mediterranean regions (Heyman et al., 2011).

The underlying causes of varying epidemiological patterns differ among regions: in western and central Europe epidemics of HFRS caused by PUUV infections follow mast years with increased seed production by beech and oak trees followed by increased rodent reproduction. In these regions human infections have a major peak in the summer and a minor peak in January–March (Heyman et al., 2001; Tersago et al., 2011). In the northern regions, hantavirus infections and HFRS epidemics occur in three to four year cycles and are thought to be driven by prey-predator interactions (Olsson et al., 2010). In Northern Europe most cases occur from late autumn to winter and in August 3–5 weeks after the summer holidays. Notably while *Myodes glareolus* is found in large parts of Europe excluding much of Mediterranean regions and the northernmost areas, human PUUV infections have not been detected in e.g. British Isles or Southern Sweden. This may be partly due to lack of diagnostics and the fact that HFRS is not a recognized entity by the local medical community (Vaheri et al., 2013a). While PUUV can experimentally infect rodents, a disease closely mimicking HFRS develops only in *Cynomolgus* ma-