

REVIEW ARTICLE

A short review of hemorrhagic fever with renal syndrome and its extra renal complications

Edmond Puca, Arben Pilaca, Pellumb Pipero, Tritan Kalo, Gentian Stroni, Elda Qyra,
Entela Y. Puca, Dhimiter Kraja

Infectious Diseases, University Hospital Center "Mother Teresa" Tirane, Albania

ABSTRACT

Hantaviruses are enveloped tri-segmented negative-stranded RNA viruses. Infection from these viruses is growing in last decades. They are causative agent for two types of diseases:

- Hemorrhagic fever with renal syndrome (HFRS), mostly observed in Eurasia and
- Hantavirus cardiopulmonary syndrome (HPS), mostly observed in American continent.

There are several Hantaviruses known to infect humans, and their main hosts are rodents. HFRS is caused from Hantaan, Dobrava, Saaremaa, Seoul and Puumala virus. The main factor, which determines the severity of Hantavirus infection, is the degree of increased permeability of infected endothelium, and the most common clinical findings in those patients are fever, headache, abdominal pains, backache, myalgia and nausea or/and vomiting. There are already numerous publications with regards to the involvement of two major systems such as renal and pulmonary in patients with HFRS. In this paper we would try to make a short review about the involvement of other organs and systems of our body in those patients. Extrarenal manifestations of Hantavirus infection include: acute ocular impairment with visual function, acute myopia, central nervous system (CNS) complications, cardiovascular impairment with myocarditis, gastrointestinal hemorrhages, but liver and pancreas may be also affected. *J Microbiol Infect Dis 2014; Special Issue 1: S54-S57*

Key words: hemorrhagic fever with renal syndrome, extra renal complications.

Renal sendromla seyreden hemorajik ateş ve böbrek dışı komplikasyonları

ÖZET

Hantavirüsler zarflı üç segmentli negatif sarmallı RNA virüslerindedir. Hantavirüslerden kaynaklanan enfeksiyonlar son dekadlarda artış gösterdi. İki farklı klinik tabloya neden olurlar: a) Renal sendromlu hemorajik ateş (HFRS), hemen tüm vakalar Avrasya'da gözlenir, b) Hantavirus kardiyopulmoner sendromu (HPS), hemen tüm vakalar Amerika kıtasında görülmektedir.

İnsanları enfekte ettiği bilinen bir çok Hantavirus vardır ve ana konakları rodentlerdir. HFRS Hantaan, Dobrava, Saaremaa, Seoul ve Puumala virus türlerinden kaynaklanır. Hantavirüs enfeksiyonlarının şiddetini belirleyen ana faktörlerin başında enfekte endoteldeki artmış permeabilite gelmektedir. En yaygın klinik belirtiler ateş, baş ağrısı, karın ağrısı, baş ağrısı, sırt ağrısı, myalji ve bulantı/kusmadır. HFRS'li hastalarda iki majör sistem olarak böbrek ve pulmoner sistemin etkilendiğine dair çok sayıda çalışma mevcuttur. Bu makalede ise HFRS'li hastalarda diğer sistem ve organların tutulumuna dair kısa bir derleme sunmak istiyoruz. Hantavirus enfeksiyonunun ekstra-renal manifestasyonları olarak görme fonksiyonunda akut bozukluk, akut miyopi, SSS komplikasyonları, myokardit şeklinde kardiyovasküler bozukluklar, gastrointestinal hemorajiler ile karaciğer ve pankreas organlarının etkilenmesi sayılabilir.

Anahtar kelimeler: Renal sendromlu hemorajik ateş, ekstrarenal komplikasyonlar

INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS) is a rodent-borne disease caused by Hantavirus.

Hantaviruses are serologically related members of the family Bunyaviridae. They are causative agent for two types of diseases: Hemorrhagic fever with renal syndrome (HFRS) in Eurasia and Hantavirus

Correspondence: Edmond Puca, Department of Infectious Diseases,
University Hospital Center "Mother Teresa" Tirane, Albania Email: edmond_puca@yahoo.com

Received: 16 May 2014, Accepted: 19 August 2014

Copyright © Journal of Microbiology and Infectious Diseases 2014, All rights reserved

cardiopulmonary syndrome (HPS) in America.¹⁻⁶ Hemorrhagic fevers have attracted more and more attention of Public Health Authorities, as an emerging pathogenic virus in the past decades.¹ China is in the top of list, with 30,000-50,000 cases reported annually, which account for >90% of total numbers worldwide. This disease is found throughout the world. Nowadays HFRS is a notifiable disease in most European countries from Balkan Peninsula to the center and north of the Europe. HFRS caused by Hantaviruses (Hantaan, Dobrava, Saaremaa, Seoul, and Puumala virus) is common in Europe and Asia. More than 10,000 individuals are reported with infection in Europe annually.²⁻⁴ However, climate change and global warming has more often modified the map of the disease and the disease seasonality. Hantaan virus (HTNV), the causative agent of HFRS that was first identified in 1978 by Lee et al.¹ Until now, 21 different Hantavirus species have been described, and more than 30 genotypes are characterized and can be found all over the world.⁶⁻⁹ The main natural reservoirs of Hantaviruses are rodents.² The distribution of these species correlates with the geographic extension of their hosts, and Hantavirus genotypes of the same geographic area are phylogenetically related.⁶⁻⁸ Infection in humans usually occurs accidentally via virus-containing, aerosolized rodent excretions such as urine, feces, or saliva. Humans do not belong to the natural host of Hantaviruses.^{1-4,7-9} People who live or work in close contact (farmers, woodcutter, hiking etc) with infected rodents are at high increased infection risk.^{6,9-13} The genus Hantavirus is roughly composed in two main groups: Old World Hantaviruses and New World Hantaviruses. HFRS in humans is caused by pathogenic Old World Hantaviruses that include: Amur virus, Seoul virus (SEO), Hantaan virus (HNT), Dobrava virus (DOBV), Tula virus (TULV), and Puumala virus (PUUV) in Europe. Hantaan virus and Dobrava virus tend to produce the most severe disease, whereas Puumala virus usually causes a less severe disease (nephropathia epidemica) a milder variant of HFRS, with a low mortality rate of 0.1%.² The first pathogenic of New World Hantavirus (Sin Nombre virus) was discovered in the early 1990s in the Four Corners region of the United States.¹⁴ From this time on, numerous additional pathogenic New World Hantaviruses were identified and characterized.²

CLINICAL PRESENTATION

HFRS shows distinctive clinical manifestations throughout the disease course, from acute influ-

enza-like febrile illness to shock syndrome. The incubation period of HFRS is between 7 to 36 days. Only 10 to 15% of cases may have a severe clinical course, with lethality rates between 6 to 15%. HFRS is characterized by a systemic involvement of capillaries and venules. Endothelial cells and monocytes are thought to be the primary cell targets of the viruses, but infection does not seem to have any direct cytopathic effects on these cells. The main factor that determines the course and the severity of HFRS is the degree of increased permeability of infected endothelium.¹⁻¹² Recent investigations suggest there might be an association between the viral RNA load and the disease severity. It induces various hemorrhagic manifestations and circulation disorders. At present, it is poorly understood how pathogenic Hantaviruses induce the capillary leakage during the acute phase of the two syndromes and why some Hantavirus species are nonpathogenic. Clinically, HFRS presents with a sudden onset of fever, headache, and myalgia, with renal impairment as the predominant organ-specific manifestation. The course of HFRS is highly variable ranging from asymptomatic to lethal outcome. The clinical course is subdivided into five stages:

- 1) Febrile stage,
- 2) Hypotensive stage,
- 3) Oliguria stage,
- 4) Diuretic stage, and
- 5) Convalescent stage.

The onset of HFRS in classical cases is with: high fever, backache, abdominal pain, chills, myalgia, malaise, and bradycardia over three to four days. Photophobia, pharynx enanthema, and a diffuse reddening of the face are also observed. On the third to fifth days, petechia develops initially on the palate. At the same time, conjunctival hemorrhages may appear and a temporary impairment of the visual function is reported. The hypotensive phase ranges 3 to 6 day after onset of fever. Shock or hypotension may occur. Laboratory findings in this phase are leukocytosis and thrombocytopenia. Patients show a wide range of renal involvements such as: tubulointerstitial nephritis, necrotizing glomerulonephritis, and IgA nephropathy. Usually, the end of the febrile stage and the early days of hypotensive stage are the time that majority of patients presented at the hospital. Duration of the hypotensive stage, determine gravity and complications of the disease also. The oliguria phase start at approximately on 8th day, and hemorrhagic manifestations become more prominent. The diuretic phase starts

at approximately on 11-13th day, and the convalescent phase lasts approximately three weeks to six months.

Extra renal manifestations include acute impairment of visual function, acute myopia, central nervous system (CNS) complications, myocarditis, and severe gastrointestinal hemorrhages. In addition, thyroid, liver, and pancreas may be also affected. Lung involvement, but to a lesser extent than in HPS is also observed during HFRS.²

Ocular findings are very common (70%) in acute PUUV-HFRS. A total of 87% had reduced visual acuity, 78% had myopic shift, 88% had decreased intraocular pressure, and 88% thickening of the lens.^{2,3} Lethal cases, in which the pituitary gland was invaded by PUUV resulting in local hemorrhages and necrosis, have been described.^{2,8} Neurological, cardiopulmonary hematologic, gastrointestinal, urogenital, ocular and pregnancy complications are prescribe in now days.¹⁻¹⁶ The clinical presentation of many patients included typical symptoms of viral encephalitis and several patients developed serious CNS-related complications.^{11,12} Orchiepididymitis is a very rare complication of HFRS by HNTV/Dobrava virus infection.^{4,13} Other authors such as Eun S Kang, Bui-Mansfield and Bren et al. are also suggested by implication of pancreas during HFRS course.¹³⁻¹⁵

The maternal and fetal outcomes of pregnancy complicated by HFRS have also been reported in China, where the most severe form of HFRS caused by Hantaan virus occurs. One of these China studies suggested there was maternal-to-fetal transmission, but any pathological and/or serological evidence did not unequivocally confirm the fetal infection). Nevertheless, in a previous report, post-natal deformity was not observed in healthy babies born naturally to mothers who recovered from HFRS.¹⁵

Treatment of Hantavirus Infections

At present, there are no antiviral drugs that are applicable to cure Hantavirus infections. The treatment of patients with HFRS or HPS is restricted based on supportive procedures to keep under control the symptoms, which may be life threatening. Patients are normally supervised in an emergency department or intensive care unit for close monitoring and care until the patient's immune system has cleared the virus and the convalescent phase begins.⁵ In our conclusion supportive therapy play a decisive role in the patients outcome.

Prevention of Hantavirus Infections

Because of the fact that infection with some Hantavirus species results in high morbidity and mortality rates, and in the view of the present situation of missing effective antiviral drugs, it is of particular importance to try to prevent such infections. It is indicated to avoid places where rodents live in large quantities, in order to avert contact with virus-containing rodent excretions.^{1,2} This includes keeping homes and the near surrounding area rodent-free, for example, by eliminating crawl spaces and debris and removing food sources to make homes and work areas unattractive for rodents.

CONCLUSION

Since the discovery of HTNV as the causative agent of HFRS, much knowledge about the various Hantaviruses and their manifestations in animals and humans has been gathered. Extrarenal manifestations in HFRS can develop at various stages, from the febrile phase to the diuretic phase. They can be associated with disease severity and occur at any stage of HFRS, and clinicians should be aware of extrarenal manifestations for early detection and close monitoring. Supportive therapy depends on the Hantavirus strain and clinical symptoms, especially it is important in HFRS and HPS, for which correction of bleeding, maintenance of BP, and treatment of renal or respiratory insufficiency may be indicated. It is hoped that a better understanding of viral biology and pathophysiology will lead to more effective and specific therapeutic modalities in the future.

REFERENCES

1. Muranyi W, Bahr U, Zeier M, van der Woude FJ. Hantavirus Infection. *J Am Soc Nephrol* 2005;16:3669-3679.
2. Vaehri A, Henttonen H, Voutilainen L, et al. Hantavirus infections in Europe and their impact on public health. *Rev. Med. Virol* 2013;23:35-49.
3. Hautala N, Kauma H, Vapalahti O, et al. Prospective study on ocular findings in acute Puumala hantavirus infection in hospitalised patients. *Br J Ophthalmol* 2011; 95:559-562.
4. Puca E, Pilaca A, Pipero P, et al. Hemorrhagic Fever with Renal Syndrome Complicated by Orchitis. *Virol. Sin* 2011;26:284-288
5. Zeier M, Handermann M, Bahr U, et al. New ecological aspects of Hantavirus infection: A change of a paradigm and a challenge of prevention-A review. *Virus Genes* 2005;30:157-180.
6. Plyusnin A. Genetics of Hantaviruses: Implications to taxonomy. *Arch Virol* 2002;147:665-682.
7. Hautala T, Sironen T, Vapalahti O, et al. Hypophyseal Hemorrhage and Panhypopituitarism during Puumala Virus Infec-

- tion: Magnetic Resonance Imaging and Detection of Viral Antigen in the Hypophysis. *Clin Infect Dis* 2002;35:96-101.
8. Kanerva M, Paakkala A, Mustonen J, et al. Pulmonary involvement in nephropathia epidemica: radiological findings and their clinical correlations. *Clin Nephrol* 1996;46:369-378.
 9. Hautala T, Hautala N, Mähönen SM, et al. Young male patients are at elevated risk of developing serious central nervous system complications during acute Puumala hantavirus infection *BMC Infectious Diseases* 2011;11:217-221.
 10. Mähönen SM, Sironen T, Vapalahti O, et al. Puumala virus RNA in cerebrospinal fluid in a patient with uncomplicated nephropathia epidemica. *J Clin Virol* 2007;40:248-251.
 11. Bui-Mansfield LT, Torrington KG, Kim T. Acute pancreatitis in patients with hemorrhagic fever with renal syndrome. *Mil Med* 2001;166:167-170.
 12. Kang E S, Lee S, Kim W, et al. Acute pancreatitis associated with haemorrhagic fever with renal syndrome. *Nephrology* 2005;10:421-425.
 13. Puca E, Pilaca A, Pipero P, et al. Hemorrhagic Fever with Renal Syndrome Associated with Acute Pancreatitis. *Virologica Sinica* 2012;27:214-217.
 14. Vapalahti K, Paunio M, Brummer-Korvenkontio M, et al. Puumala virus infections in Finland: increased occupational risk for farmers. *American Journal of Epidemiology* 1999;149:1142-1151.
 15. Kim BN, Choi BD. Hemorrhagic Fever with Renal Syndrome Complicated with Pregnancy: A Case Report. *The Korean Journal of Internal Medicine* 2006;21:150-153.
 16. Avsic-Zupanc T, Petrovec M, Furlan P, et al. Hemorrhagic fever with renal syndrome in the Dolenjska region of Slovenia—a 10-year survey. *Clin Infect Dis* 1999;28:860-865.
 17. Roig IL, Musher DM, Tweardy DJ. Severe Pulmonary Involvement in a Case Attributed to Domestically Acquired Seoul Hantavirus in the United States *Clinical Infectious Diseases* 2012;54:91-94.