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HANTAVIRUS- A CHALLENGE OF PREVENTION

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Abstract:

Hantaviruses are rat infections that havebeen distinguished as etiologic specialists of 2 ailments of people: hemorrhagic fever with renal disorder (HFRS) and hantavirus aspiratory disorder (HPS). This article presents a succinct survey of hantavirus science, the clinical highlights of HFRS and HPS, and tests for the discovery of hantavirus diseases in people. Information Synthesis.— Hemorrhagic fever with renal disorder is an ailment found outside the Americas and means a gathering of clinically comparative diseases that fluctuate in seriousness comparative with the causative specialist. Hantavirus aspiratory disorder is related with higher mortality than HFRS, was first perceived as a hantavirus infection in 1993, and happens inside the American mainlands. Ongoing hereditary examinations show that both Old and NewWorld hantavirus species coevolved with explicit rat has. The rundown of unmistakable hantaviruses related with HPS is developing. The thriving human populace is causing disturbance of characteristic natural surroundings as increasingly more land is cleared for business and private purposes. Numerous rodents promptly adjust to life in human settlements, where they for the most part profit by decreased predation and where they here and there multiply to high numbers.

Keywords: Hantavirus, HFRS, HPS, Pulmonary Syndrome

Introduction:

Hantaviruses are emerging yet neglected viruses of the Bunyaviridae family harbored by small mammals. They are known to cause life-threatening diseases in humans in Eurasia and the Americas.[1,2]

Hantavirus disease came toglobal attention when two major outbreaks were reported during the last century. The first, anHFRS outbreak, occurred during the Korean War (1950 to 1953), when more than 3,000United Nations troops fell ill. The second was an outbreak of HPS that occurred in theFour Corners region of the southwestern United States in 1993. Hantaviruses remain aglobal threat to public health; they have been estimated to affect approximately 200,000humans annually worldwide in recent years. Moreover, the number of countries reportinghuman cases of hantavirus infection is still on the rise.[3,4]

Like other viral members of the *Bunyaviridae*family, hantaviruses are enveloped RNA viruses that contain three-segmented negative-sense RNAs, designated S, M, and L based on the molecular weight of their virion. The S, M, and L RNA segments encode nucleocapsid protein (N), envelope glycoproteins (Gn and Gc), and RNA-dependent RNA polymerase (L) protein, respectively.[5,6]Recently, a large number of shrews and moles (order Soricomorpha/Eulipotyphla) and bats (order Chiroptera) have been identified as reservoirs of additional hantaviruses.[7,8]

Old World and New World Hantaviruses:

The genus Hantavirus is roughly composed of two maingroups: Old World and New World hantaviruses. HFRS inhumans is caused by pathogenic Old World hantaviruses thatinclude Amur virus, Seoul virus, and HTNV, the epidemiologicallymost important species, with lethality rates up to 15% inAsia, as well as Dobrava virus (DOBV), Tula virus (TULV), andPuumala virus (PUUV) in Europe; the last one is the mainhantavirus species in Europe and induces Nephropathiaepidemica(NE), a milder variant of HFRS, with mortality rates of0.1% (10,20). HFRS affects approximately 200,000 people eachyear predominantly in Asia. In 2004, 235 cases were reported inGermany according to a recent epidemiologic bulletin of

theRobert-Koch Institute.The first pathogenic New World hantavirus (Sin Nombrevirus) was discovered in the early 1990s in the Four Cornersregion of the United States. From this time on, numerousadditional pathogenic New World hantaviruses were identifiedand characterized. New World hantaviruses are thecausative agent of approximately 300 cases of HPS each year inNorth and South America, with lethality rates up to 50%.Human hantavirus infections are assumed to occur accidentally,and men represent a dead end for the hantavirus lifecycle. Transfer of virus particles from infected to uninfectedpeople normally does not occur. One exception is the Andeshantavirus strain Sout in Argentina, of which sporadicalperson-to-person transmissions were reported. Thisfinding reveals a worrying risk potential of hantaviruses forhuman health.[9]

Insectivore-borne hantaviruses:

Although several studies have shown the presence of antibodiesthat cross-react with Eurasian hantaviruses in African populations,until 2006 the African continent was a blank spot onthe hantavirus map [59]. The first African hantavirus was namedSangassou virus and was found in African wood mouse, Hylomyscussimus.[10,11]More recently, hantavirus RNA sequences have been detected in bats from western Africa. The presence of newly described hantaviruses in insectivores and bats has challenged the conventional view that hantaviruses originated from rodents, and suggests there may be additional unrecognized hantaviruses circulating in a wide range of animal hosts.[12]

Current Status:

Currently, three laboratory infection systems have been developed to study hantavirus infections of reservoir hosts: Seoul virus (SEOV) infection of the Norway rat (Rattus norvegicus), Puumala virus (PUUV) infection of the bank vole (Myodesglareolus), and Sin Nombre virus (SNV) infection of the deer mouse (Peromyscus maniculatus).[13,14]

According to the presence of infected animal hosts and their contacts to humans, occurrence of hantavirus disease can be observedin different climatic zones including subtropics and tropics. Hantaviruses are considered to belong to the group of emerging viruses;this has mainly to do with the frequent identification of novel hantaviruses and their role as human pathogens. There are differenttrends in the development of case numbers; whereas in China – thecountry with most HFRS cases per year worldwide – the number ofpatients seems to decrease because of the vaccination approachesin this country, the number of cases in Europe and particularlyGermany shows a clear increase over the last years.[15]

HANTAVIRUSES[16]			
Virus	Original source	Source Location	Disease
Murinae subfamily associated viruses			
Hantaan	Apodemusagrarius	Korea	HFRS
Seoul	Rattus norvegicus, Rattus rattus	Korea	HFRS
Dobrava-Belgrade	Apodemusflavicollis	Slovenia	HFRS
Thai-749	Bandicotaindica	Thailand	Unknown
Arvicolinae subfamily associated viruses			
Puumala	Clethrionomysglareolus	Finland	HFRS
Prospect Hill	Microtus pennsylvanicus	Maryland	Unknown
Tula	Microtus arvalis	Russia	Unknown
Khabarovsk	Microtus fortis	Russia	Unknown
Topografov	Lemmussibiricus	Siberia	Unknown
Isla Vista	Microtus californicus	California	Unknown

Sigmodontinae subfamily associated viruses			
Sin Nombre	Peromyscus maniculatus	New Mexico	HPS
New York	Peromyscus leucopus	New York	HPS
Black Creek Canal	Sigmodonhispidus	Florida	HPS
Bayou	Oryzomys palustris	Louisiana	HPS
CañoDelgadito	Sigmodonalstoni	Venezuela	Unknown
Rio Mamore	Oligoryzomysmicrotis	Bolivia	Unknown
Laguna Negra	Calomyslaucha	Paraguay	HPS
Muleshoe	Sigmodonhispidus	Texas	Unknown
El Moro Canyon	Reithrodontomysmegalotis	California	Unknown
Rio Segundo	Reithrodontomysmexicanus	Costa Rica	Unknown
Andes	Oligoryzomyslongicaudatus	Argentina	HPS
Insectivore associated virus			
Thottapalayam	Suncusmurinus	India	Unknown
Other hanta virus rodent pairs			
Monongahela	Peromyscus maniculatus	Unknown	Unknown
Blue River	Peromyscus leucopus	Unknown	Unknown
Oran	Oligoryzomyslongicaudatus	Unknown	Unknown
Lechiguanas	Oligoryzomysflavescens	Unknown	Unknown
Bermejo	Oligoryzomyschacoensis	Unknown	Unknown
Maciel	Bolomys obscurus	Unknown	Unknown
Pergamino	Akadonazarae	Unknown	Unknown

Transmission:

These viruses spread when the vector mosquitoesor tick bites a human, or when ticks are crushed by human. In somecases, the humans may get infected when they care for or slaughter these animals.[17]Also transmitted by rodentsof the family Muridae. They cause hemorrhagic fever with renal syndrome (HFRS) and hantaviruspulmonary syndrome (HPS). These diseases are mainly associated with rural areas, as infection inhumans occurs following the inhalation of aerosolized feces, urine, and saliva of infected rodents.[18]

Hentavirus associated diseases:

Hentavirus Pulmonary Syndrome:

As of December 1999, 32 cases of Hantaviruspulmonary syndrome had been reported inCanada, predominantly in western Canada,with British Columbia and Alberta reportingthe largest numbers of cases.[19] At the Universityof Alberta Hospital, 20 patients withHantavirus pulmonary syndrome presentedfrom 1989 to 1999.[20] Verity et al. describedthe clinical and laboratory findings of 19 of the20 patientsand identified two broad categoriesof Hantavirus pulmonary syndromeclinically and radiologically: a rapidly progressive,fulminant, and often fatal clinical formwith radiographic features of rapidly progressivealveolar pulmonary edema, air-space consolidation,and pleural effusions; and a limited,less severe clinical form usually associatedwith radiographic features of mild interstitialedema and minimal air-space disease. All patientswith the limited form of Hantavirus pulmonarysyndrome survived the illness, whereas46% of those with the fulminant form died.[21]

Hemorrhagic fever with renal syndrome:

The clinical course of HFRS is primarily characterized by fever, circulatory collapse with hypotension, hemorrhage, and acute kidney injury (AKI). The disease typically progresses through five phases: febrile, hypotensive shock, oliguric, polyuric, and convalescent. Additionally, some of these phases frequently overlap in severe cases, and one or two phases are frequently absent in some mild cases. Laboratory findings during acute stage of the disease are anemia, leukocytosis, thrombocytopenia, elevated liver enzymes, and serum creatinine (renal dysfunction), as well as proteinuria and hematuria. Most of the cases can recover completely, while some severe cases still have some sequelaes including headache, insomnia, hyperhidrosis, hemorrhage, and hyperdiuresis. Kidney injury frequently occurs in HFRS and the most prominent pathological presentation is acute tubulointerstitial nephritis following the infiltration of inflammatory cells.[23] AKI often induces death in patients with HFRS, particularly in the oliguric phase.[24]The elderly patients often develop severe AKI and are more likely to have shock, hematuria, thrombocytopenia and leukocytosis. The patients with severe AKI usually need dialysis or continuous blood purification and stay longer in hospital than non-AKI patients. Thrombocytopenia, which is one of the factors that cause the increase of blood vessel permeability, is related to severe AKI among patients with acute HTNV infection. Acute thrombocytopenia is a common symptom of HFRS and persists throughout hantavirus infection. Therefore, thrombocytopenia is an important basis for the diagnosis of HFRS. Pulmonary, cardiac, endocrinological, central nervous system, and ocular findings are also major manifestations of HFRS. The febrile, hypotensive, and oliguric phases can overlap in somesevere cases. In this condition, acute progressive noncardiogenicpulmonary edema, which often presents as acute respiratorydistress syndrome (ARDS), is likely to happen, and, thus, resultsin a high fatality rate. It was demonstrated that the agitation,conjunctival hemorrhage, coma, were also negatively correlatedwith survival outcome.[25]

Hantavirus pathogenesis:

The primary target cells of hantavirus infection are endothelial cells of capillaries of various organs, primarily of the lung and kidneys, although infection occurs in a variety of other organs and cell types (endothelial and epithelial cells, macrophages, follicular dendritic cells, lymphocytes, neutrophils and platelets). The main receptor in endothelial cells for pathogenic hantavirus is beta-3-integrin. Infection is followed by impairment of the barrier function of endothelial cells, fluid extravasation and subsequent organ failure. However, although appearance of neutralising antbodies (NAbs) seems to impair the development of disease (see below), the mechanisms for the so-called “vascular leak” are largely unknown. Notably, infection of endothelial cells by hantavirus is noncytopathic in vitro and in vivo, which has led to the hypothesis that a strong cellular immune response, elicited by cytotoxic CD8+ T cells, may be responsible for hantavirus pathogenesis in man.[26]

The basic mechanisms behind HFRS pathogenesis also relate to increased vascular permeability, and as noted above, the causative agents infect endothelial cells without cytopathic effects. There has not been a proper animal model for HFRS, and the Syrian hamster model for ANDV and HPS is not applicable for HFRS.[27] However, cynomolgus monkeys infected with wild-type PUUV strains (not cell culture adapted) produce NE-like disease symptoms and clinical pathology, including elevations of nitric oxide, various cytokine (IL-10, IL-6, and TNF-), and C-reactive protein levels. In histological studies of animals, viral antigen and RNA detected by in situ hybridization and nucleocapsid protein detected by immunohistochemical staining were observed in kidney, spleen, and liver tissues. In the kidneys, the virus-infected cells colocalized with inflammatory cell infiltrations and tubular damage, and these infiltrations contained mainly CD8-type T cells. These findings are similar to those reported for human kidney tissues of NE patients, suggesting that viral replication together with the immune response are involved in tissue injury. Importantly, there is a genetic predisposition toward severe HFRS disease related to HLA type.[28]

Diagnosis:

Laboratory diagnosis of hantavirus infection:

The diagnosis of hantavirus infection in humans is based on clinical and epidemiological information as well as laboratory tests. A definitive diagnosis cannot be based solely on clinical findings, especially in cases where disease is mild to moderate. Laboratory testing should be performed on samples from patients with fever of unknown origin, severe myalgia, thrombocytopenia, renal failure or respiratory distress, and patients living in hantavirus disease-endemic regions, or persons with recent outdoor activities during which there was possible exposure to rodents or their excreta. Because hantaviruses differ in their geographic distribution, course of infection and likely outcome, specific and accurate laboratory diagnostic tests are important. Laboratory diagnosis of hantavirus infection is based on four primary categories of tests: serology, reverse transcription (RT)-PCR, immunochemistry and virus culture.[29]

Serological tests:

Human serum was tested by means of IgM-ELISA and IgGELISA using a recombinant nucleocapsid protein from ARAV as the antigen, as previously reported. The rodent blood was also tested by means of IgG-ELISA using the same technique, but changing to a mixture that included anti-Peromyscus and anti-mouse peroxidase conjugates.[30]

reverse transcription (RT)-PCR:

Hantavirus diagnosis using cell culture is tedious and takes along time. To specifically analyze the neutralizing capacity of the patient serum, a plaque reduction neutralization test or a focal reduction neutralization test could be used. Common measures to diagnose hantavirus infections utilize serology, since on admission, most patients have both specific immunoglobulin M (IgM) and IgG. Sensitive and specific detection of hantavirus in patient specimens can be monitored by reverse transcriptase (RT) PCR. Recently, real-time RT-PCR techniques have been used for detection of PUUV in tissue culture. In our efforts to follow a PUUV infection in vivo, we used a one-step real-time RT-PCR method for the detection of PUUV RNA in NE patient sera from northern Sweden. The technique was useful to determine the level and duration of viremia in NE patients and to identify patients with PUUV infection before the appearance of antibodies.[31]

immunochemistry and virus culture:

A wide array of technologies have been used to detect antibodies to hantaviruses, using cultured and/or purified native-virus preparations or recombinant proteins expressed in bacteria, yeast or insect cells.[32] Both indirect fluorescent assay (IFA) and enzyme immunoassay (EIA) are widely used for detection of specific IgM or low-avidity IgG antibodies. IgM detecting methods are important tools for diagnosis of acute infections, especially in endemic areas with a high prevalence of virus-specific IgG due to previous infections.[33] The μ-captured ELISA to detect IgM antibodies, using viral native or recombinant N antigens, should be preferred because it is superior to IFA and solid phase ELISA in terms of sensitivity.[34] Western blot assays can be used, which are generally in agreement with those of the IgMcapture format for acute infections.[35,36] In addition, the immunochromatographic 5-min IgM-antibody test has been developed for rapid diagnosis.[37] The IFA test remains popular in Europe and Asia, perhaps in part because it is so easily performed, but such tests are intrinsically limited by problems with specificity, especially with inexperienced users.[38] Although ELISA is optimal for a highly specific serological confirmation of hantaviral infections, the antibody responses usually cross-react strongly between different hantaviruses, indicating that ELISA or other serological tests such as IFA or immunoblotting cannot be used for serotyping.[39] The plaque reduction neutralization test (PRNT) is considered to be the gold standard serological test and, it can be used to discriminate between different species of Hantavirus. However, the PRNT test with infectious hantavirus should be done in a biosafety level-three laboratory, which is a serious limitation for many investigators.[40] For post-mortem confirmations, detection of hantavirus antigens can be done by immunohistochemistry testing of formalin-fixed tissues with appropriately specific monoclonal or polyclonal antibodies.[41]

Incubation Period:
The incubation period for HFRS can range from approximtely one to 6 weeks, while incubation periods of 1- 7 weeks have been reported in HPS. Many cases of HFRS and HPS seem to become apparent in about 2-3 weeks.[42]

Clinical Signs:
Hantaviruses usually cause one of two syndromes, HFRS or HPS; however, clinical cases that have attributes of both HFRS and HPS are occasionally reported, and some people experience only a nonspecific febrile illness. Asymptomatic infections also occur.[43]

Hantavirus Treatment:
Currently, no Food and Drug Administration approvedantiviral drug or immunotherapeutic agent is available fortreatment of the hantavirus diseases.[44]
Ribavirin
ribavirin for treatment ofpresumed HPS provides the most complete informationon adverse events temporally associated withintravenous ribavirin available to date.[45] In spite of theuse of intravenous ribavirin for Lassa fever and HFRSpatients abroad, this study of HPS patients representsby far the largest experience at this dosage underconditions permitting close observation of patientswith accompanying clinical laboratory support.Adverse clinical events associated withribavirin (anaemia, chills/rigors, elevated serum uricacid and hyperbilirubinaemia) occurredin temporal association with drug receipt at essentiallyequal rates among HPS and non-HPS patients.[46]
Lactoferrin
Hantaviral foci number, in cultured cells infected with SR-11, was reduced with bLf treatment. Mechanisms of anti-hantaviral activities of bLf and ribavirin (Rbv) were also investigated. Preincubation of cells with bLf before infection inhibited hantavirus focus formation of 85% whereas post infection treatment with Rbv inhibited the focus formation of 97.5%.[47] Conversely, other in vitro experiments showed that Hantaan hantavirus, the prototype hantavirus, is insensitive to several antiviral salivary proteins, and is partly resistant to the antiviral effect of saliva. It has been found that combined bLf and Rbv treatment completely prevented focus formation. Consequently, in in vivo studies, bLf pre- and Rbv post-treatment were evaluated in suckling mice infected with hantavirus, of which 7% survived.[48] Lactoferrin administered before viral challenge improved survival rates to up to 70% for single administration and up to 94% for double administration. Rbv gave survival rates up to 81%. These results suggested that both lactoferrin and Rbv were efficacious in the treatment of hantavirus infection in vivo.[49]

Favipiravir:
favipiravir against Sin Nombre virus (SNV) and ANDV, the predominant causes of HPS in North and South America, respectively.[50] *In vitro*, T-705 potently inhibited SNV and ANDV, as evidenced by decreased detection of viral RNA and reduced infectious titers. For both viruses, the 90% effective concentration was estimated at ≤5 μg/ml (≤31.8 μM). In the lethal ANDV hamster model, daily administration of oral T-705 at 50 or 100 mg/kg of body weight diminished the detection of viral RNA and antigen in tissue specimens and significantly improved survival rates. Oral T-705 therapy remained protective against HPS when treatment was initiated prior to the onset of viremia.[51]

Corticosteroids:
Hantaviruses can be associated with severe form of hemorrhagic fever with renal syndrome although there are only a few cases reporting chronic kidney disease after hantavirus infection.[52] We report a severe nonresolving chronic renal failure after protracted Dobrava hantavirus infection successfully treated with corticosteroids. Ten days after working in a basement a 33-year-old man fell seriously ill, with high fever, chills, diffuse myalgia, headache and abdominal pain. After hospital admission a diagnosis of hemorrhagic

fever with renal syndrome caused by Dobrava hantavirus was made. Acute oliguric kidney injury developed in the first 3 days after admission, in a few days diuresis restored and he became polyuric.[53]

Monoclonal Antibodies:

Monoclonal antibodies are important tools for various applications in hantavirus diagnostics. Recently, we generated Puumala virus (PUUV)-reactive monoclonal antibodies (mAbs) by immunisation of mice with chimeric polyomavirus-derived virus-like particles (VLPs) harbouring the 120-amino-acid-long amino-terminal region of the PUUV nucleocapsid (N) protein.[54]

Prevention:

For the prevention of hantavirus diseases,human habitations showing signs of rodent activityshould be decontaminated, and steps should be taken torid the premises of the offendinganimals. Decontaminationin many cases can be accomplished by soaking theaffected area with a 10% (v/v) solution of house hold bleach.

Conclusion:

In the course of recent decades, the comprehension and acknowledgment of hantaviral contaminations through the world has incredibly improved. The quantity of perceived infections keeps on expanding, as does the range of hantaviral diseases. Despite the fact that recently distinguished, Hantavirus is an old sickness. Ecological changes may influence the geographic conveyance, wealth, and elements of the rat transporter, and henceforth the study of disease transmission of hantavirus contaminations. It is commonly acknowledged that hantaviruses are dispersed around the world, yet the appropriation of explicit infection stays to be additionally researched. With the advancement of progressively fast and delicate tests, and expanded clinician mindfulness, human hantaviral diseases will probably be recognized in new zones, and new rat species may be found to convey yet obscure infections. There is as yet far to go to locate a successful treatment for hantavirus contaminations, and the long haul guess of hantaviral diseases and the pathogenicity of certain infection species stay to be set up. Anticipation can be halfway accomplished by rat evasion, yet genuine security will require a protected and successful multivalent antibody or an immunization adjusted to nearby conditions.

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