ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 4 Issue 1 January 2021

Review Article

Diagnosis, Virology and Treatment for Hantavirus Pulmonary Syndrome (HPS): A Challenging Sickness to Human Health

Soumitra Sahana[1]*, Sk Abdur Rahamat[1], Indranil Chatterjee[2], Rajeswar Das[2], Suman Kumar Nath[2], Snehansu Biswas[2] and Sanchari Chatterjee[2]

[1]B. Pharm, Birbhum Pharmacy School, Birbhum, West Bengal, India

[2]Assistant Professor, Birbhum Pharmacy School, Birbhum, West Bengal, India

***Corresponding Author:** Soumitra Sahana, B. Pharm, Birbhum Pharmacy School, Birbhum, West Bengal, India.

Received: September 01, 2020

Published: December 09, 2020

Abstract

Hantaviruses are rodent viruses that have been realize as etiologic dealers of two illnesses of humans: HFRS (hemorrhagic fever with renal syndrome) and hantavirus pulmonary syndrome (HPS). This article gives a concise overview of hantavirus biology, the scientific aspects of HFRS and HPS, and checks for the detection of hantavirus infections in humans. Together, these viruses have yearly precipitated about 200,000 human infections global in current years, with a case fatality fee of 5 - 15% for HFRS and up to 40% for hantavirus cardiopulmonary syndrome (HCPS). The high fee of mortality ought to be decreased if advantageous therapeutics ought to be observed for cure of this illness. There is presently no wonderful remedy reachable for both HFRS or HCPS. In this paper, we summarized the Virology, Epidemiology of HFRS and HCPS, Diagnosis, and Treatment of hantaviruses disease.

Keywords: Hantavirus; Hemorrhagic Fever with Renal Syndrome (HFRS); Hantavirus Pulmonary Syndrome (HPS); Hantavirus Cardiopulmonary Syndrome (HCPS); Virology; Epidemiology; Diagnosis; Treatment

Introduction

In latest years, the repeated outbreak of hantavirus sickness has brought about a serious chance to human health. The spread of hantavirus from herbal hosts to people is a herbal ecological process; however, the outbreak of hantavirus is pushed by way of striped discipline mouse populace cycle dynamics and seasonal local weather trade [1]. Humans end up contaminated by way of both inhaling virus contaminated aerosols or having contact with the urine or droppings of contaminated animals [2]. Hantavirus, basically transmitted by way of rodent animals, more often than not via urine, feces, and saliva and the aerosols produced by way of them, however hardly ever by using the bites of contaminated animals by way of rodent animals, more often than not via urine, feces, and saliva and the aerosols produced by way of them, however hardly ever by using the bites of contaminated animals [3]. In current years, the contamination fee of hantavirus has multiplied in China and Europe [4]. There are presently no licensed vaccines or therapeutics for hantavirus infection; however, medical trials have commenced the usage of energetic immunization of experimental DNA vaccines [5]. Hantaviruses are endemic international and labeled into two exceptional companies based totally on geography and pathogenesis of infection. Old World hantaviruses, together with Hantaan, Puumala, Seoul, and Dobrava, motive hemorrhagic fever with renal syndrome (HFRS) with a 1% to 15% mortality charge and 100,000 to 150,000 instances per yr [6]. Infectious illnesses are the main motive of fever in Indonesia. Since the scientific displays of frequent tropical illnesses are frequently challenging to differentiate, and for the reason that correct diagnostic equipment are missing in many healthcare settings, misdiagnosis can effortlessly occur, main to inappropriate scientific management. As dengue and typhoid fever are predominant in Indonesia, different etiologies such as hantavirus (HTV) contamination are regularly omitted and hardly ever recognized [7]. In Europe, the infection commonly manifests as a slight structure of haemorrhagic fever with renal

syndrome, known as nephropathia epidemica (NE). It is a zoonotic disease, brought on by means of the virus species 'Puumala' and transmitted to people by way of bank voles (*Myodes glareolus*). Globally, between one hundred fifty zero and 200 zero sufferers are hospitalized every 12 months due to HFRS [8]. Hantaviruses do no longer reason large pathological effects, suggesting that immune mechanisms alternatively than direct viral cytopathology can provide an explanation for the complicated pathogenesis of haemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). Currently, it is assumed to be a multifactoral method and consists of T-cell mediated endothelial damage, immune effectors, cytokines and chemokines, as properly as a ß3-integrin (used by means of pathogenic hantaviruses as receptors) dysfunction-mediated amplify of vascular permeability [9]. Hantaviruses first came to the interest of western medication in the early 1950s when greater than 3000 US troops struggle in the Korean war became unwell with Korean hemorrhagic fever, which later got here to be recognized as HFRS. The wave of HFRS instances possibly resulted from a excessive contact price with rodents chronically contaminated with Hantaan virus (HTNV) as troopers lived and fought in the open fields. The 2nd category of illness, HPS, was once first diagnosed in 1993 when an outbreak of extreme respiratory sickness struck in the Four Corners region of the US [10].

Hantavirus virology

Despite heterogeneous scientific pix and distinctive host reservoirs, hantaviruses have comparable genomic organization, and RNA-encoded proteins share excessive stages of sequence homology [11]. Hantavirus exhibit the genus Hantavirus in the household Bunyaviridae [12]. Genetic float takes place via accumulation of factor mutations (through the genome) and small insertions/deletions (in the noncoding regions). Reassortment of genome RNA segments appears to appear a great deal greater regularly than recombination [13]. Genetic range in hantaviruses is generated by means of genetic drift, reassortment of genome RNA segments, and recombination [14]. Hantavirus sorts a genus internal the family Bunyaviridae. Hantaviruses, now not transmitted by using the usage of biting insects). It has a segmented RNA genome which is single stranded, horrific trip. The genome segments are designated Small, large, medium. The large segment encodes an RNA polymerase. The M section encodes two surface G1 and G2, glycoproteins. The small segment encodes the nucleoprotein which varieties the filamentous helical nucleocapsid that offers the virus its tessellated appearance. Unlike different RNA viruses with a segmented genome (e.g., influenza A, rotavirus) there is little proof of viral genome reassortments [15]. Although hantavirus used to be first cultured in human cells, more than a few vero mobilephone strains (E6 or C1008) are more sensitive for growth. Unlike different negative-strand RNA viruses, hantaviruses do no longer possess an M- or matrix protein that commonly orchestrates virus assembly. During culture, granular or filamentous inclusion our bodies appear in the cytoplasm [16,17]. A most possibility phylogenetic tree of the entire amino acid and DCP sequence of the M phase of hantaviruses was once made based totally on the global Committee on Taxonomy of Viruses up to date taxonomy of the order Bunyavirales in 2019 (Figure 1).

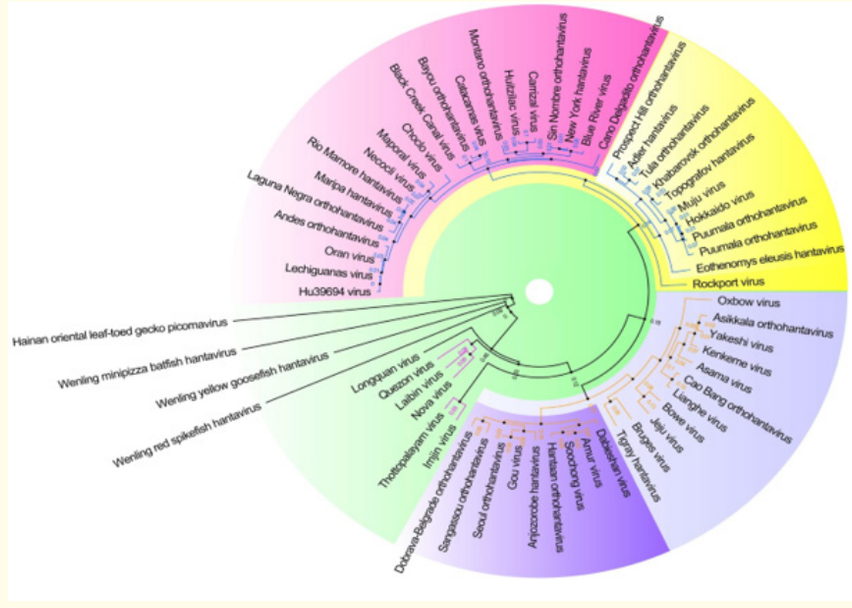

Figure 1: PCR products of the DNA amplicons of IL-4 visualized by 1% agarose gel electrophoresis, for 1 hour in (50V), product sizes were determined by comparison with 2000 bp marker. Lane L: 2000 bp DNA marker, lanes 1-12: IL-4 bands.

This phylogeny suggests the modest genetic range of the virus family. The diameter of hantavirus particles is 80–US210 nm, and the shape is spherical or ovoid. They are composed of 20 - 30% fat, > 50% protein, 7% carbohydrates, and 2% RNA. They are very secure and can live to tell the tale for extra than 18 days at 4°C and -20°C and 10 days at room temperature [18].

The epidemiology of HFRS and HCPS

China has the easiest incidence and mortality of HFRS in the world, accounting for greater than 90% of the whole variety of HFRS instances in the world. The distribution map of hantavirus instances pronounced in latest Chinese literatures is summarized in figure 2. More than 90% of the whole instances have been clustered in 9 provinces and more often than not said in spring and autumn–winter seasons. We can have a look at that the annual common range of cases in Shaanxi Province was once greater than 2000, rating at the pinnacle of the listing (Figure 2).

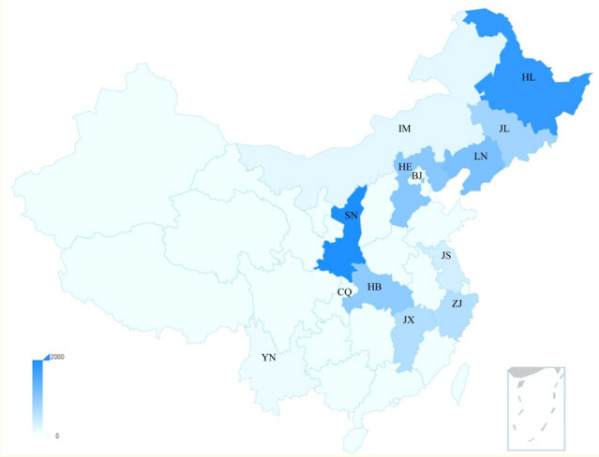

Figure 2: The distribution map of the common hantavirus instances in China of current years. The major provinces proven in the map had been Heilongjiang: HL; Shaanxi: SN; Hebei: HE; Liaoning: LN; Hubei; HB; Jilin: JL; Jiangxi: JX; Zhejiang: ZJ; Jiangsu: JS; Inner Mongoria: IM; Beijing: BJ; Yunnan: YN; Chongqing: CQ. The bar represents the annual common range of cases. These records had been posted by using Chinese literatures.

From 2006 to 2017, Shaanxi has steadily come to be the province with the perfect incidence in China, with about 4.51 cases/100,000 cases, of which extra than 90% are focused in the central location (Xi'an, Xianyang, Baoji, and Weinan cities) [19]. From 2006 to 2012, a complete of 77,558 instances and 866 deaths had been stated with the common annual incidence price of 0.83 per 100,000, mortality fee of 0.01 per 100,000 and case fatality fee of 1.13%. So far, HFRS instances have been suggested in 30 out of 32 provinces in China (excluding Hong Kong, Macao, and Taiwan) [20]. It is probably that instances of HPS will make bigger as the human populace continues to encroach on undeveloped land in the Americas. Unfortunately, rodents such as P maniculatus are regarded appealing ("cute"), and there is a temptation to preserve them as pets or to feed free-ranging animals, things to do that must continually be discouraged. Since they are possible carriers of hantaviruses (and different pathogens), wild mice and rats have to be dealt with solely through skilled specialists sporting protecting apparel, consisting of respirator masks geared up with N-100 filters (N-100 filters are the new designation for high-efficiency particulate-arresting [HEPA] filters). For the prevention of hantavirus diseases, human habitations displaying symptoms of rodent pastime have to be decontaminated, and steps must be taken to rid the premises of the offending animals. Decontamination in many instances can be completed with the aid of soaking the affected place with a 10% (v/v) answer of family bleach. The consciousness that Andes virus can be transmitted man or woman to individual [21,22]. More than half of the North American hantavirus instances appear in the Four Corners area of the Southwest, however infections have been said in 34 US states. Although normally going on in rural areas, up to 25% of cases occur in city and suburban areas [23]. Although reporting of the disorder seems pretty sparse, the actual incidence can also be rather greater due to asymptomatic infections. In a find out about carried out in Baltimore (an place with very few reported instances of HCPS), 44% of mice and 0.74% (9 patients) were serologically high quality for hantavirus notwithstanding being in any other case healthy and asymptomatic. Although there seems to be a significant spectrum of disease, the case fatality price for symptomatic HCPS patients in the United States is 38% [24]. Given the close affiliation with these danger factors, prevention of publicity to rodents or rodent droppings is essential. Those dwelling in areas with known populations of provider rodents need to reduce contact by eliminating hospitable rodent environments, sealing gaps in homes and outbuildings, putting traps to discourage rodent infestation, removing possible nesting sites, and right now disposing of leftover food and rubbish [25].

Diagnosis of hantavirus

The analysis of hantavirus contamination in people is based totally on medical and epidemiological data as properly as laboratory

tests. A definitive prognosis can't be primarily based fully on medical findings, specially in instances the place sickness is moderate to average [26,27]. Laboratory checking out need to be carried out on samples from sufferers with fever of unknown origin, extreme myalgia, thrombocytopenia, renal failure or respiratory distress, and sufferers residing in hantavirus disease-endemic regions, or individuals with current outside things to do in the course of which there used to be viable publicity to rodents or their excreta [28,29]. Because hantaviruses fluctuate in their geographic distribution, direction of contamination and in all likelihood outcome, particular and correct laboratory diagnostic checks are necessary [30]. Laboratory analysis of hantavirus contamination is primarily based on 4 principal classes of tests: serology, reverse transcription (RT)-PCR, immunochemistry and virus culture. The most sensible method for the laboratory prognosis of hantavirus contamination is based totally on serologic checks [31-33]. The three structural proteins of hantaviruses (Gn, N and Gc) can set off a excessive degree of IgM antibodies, which are detectable at the onset of symptoms [34]. Nevertheless, hantavirus contamination in people in Colombia has no longer been recognized via tradition or molecular techniques. The eventual discovering of this first medical case of hantavirus contamination in Colombia is regular with the excessive occurrence of hantavirus antibodies in human beings in the place and the in all likelihood publicity of the affected person to rodents. Furthermore, the medical presentation was once comparable to that discovered in neighbouring Panama [35]. This new assay used to be exceptionally particular and sensitive; a analysis of NE may want to be tested or excluded hastily from an early single serum sample. With this check we have now confirmed the prognosis of NE in extra than 1300 Finnish sufferers for the duration of 22 months in 1989-91 [36]. Sensitivity, specificity, and high quality and terrible predictive values had been decided from ROC evaluation for findings of magnitude in the prognosis of leptospirosis, and a scoring machine for analysis was once developed ("MICE" score) [37]. A prognosis of hantavirus was once regarded due to the shut resemblance of symptomatology with leptospirosis, even though it is very sometimes said [38]. Timely identification of current tour or publicity to rodents and their habitats is imperative. Initial chest radiographs will disclose authentication of pulmonary edema in roughly one-third of sufferers with hantavirus cardiopulmonary syndrome. Within forty eight hours, almost all sufferers will have interstitial edema, many will have pleural effusions, and two-thirds of them will display widespread bibasilar or perihilar airspace sickness [39].

- A febrile sickness (i.e. temperature N101.0° F (N38.3°C) designate by bilateral communicate interstitial edema that may also radiographically resemble ARDS, with respiratory understand requiring supplemental oxygen, creating inside seventy two hours of hospitalization, and occurring in a formerly healthful person.
- An unexplained respiratory sickness ensuing in death, with an autopsy examination demonstrating noncardiogenic pulmonary edema besides an identifiable cause.

Because confirmatory checking out is frequently no longer without delay available, a peripheral blood smear may additionally facilitate a extra well timed diagnosis. If pulmonary edema is evident radiographically in a formerly healthy patient with a suspected publicity or tour history, the presence of 4 of 5 of the following standards used to be proven to be 96% touchy and 99% specific for Hantavirus: myelocytosis, increased than 10% immunoblasts, hemoconcentration, thrombocytopenia, and the skives of toxic granulations in neutrophils [40].

- Leukocytosis with neutrophilia, a left shift (possibly as excessive as 50%) and unusual lymphocytes.
- Platelet rely much less than 150000.
- Elevated serum creatinine tiers (reported in about 15% of all patients).
- Proteinuria.
- Mild elevations of transaminases, CPK, and amylase have been reported.
- CDC: "The aggregate of ordinary lymphocytes, a significant anemia, and thrombocytopenia in the putting of pulmonary edema is salacious of a hantavirus infection". HCPS terrible prognostic indicators.
- Falling serum albumin, hemoconcentration, and a good sized decline in the platelet remember advise a fluid shift from the systemic circulation to the lungs.
- Metabolic acidosis in mixture with rising serum lactate (N4.0 mmol/L) and extended PT and PTT.
- Disseminated intravascular coagulation may additionally not often take place in severe cases of HCPS; however, this is a good deal much less frequent than in hemorrhagic fever next to renal syndrome.

Because HCPS and ARDS share many overlapping characteristics, formal hantavirus trying out at a reference laboratory is solely

encouraged for formerly wholesome sufferers except predisposing medical conditions such as persistent obstructive pulmonary disease, malignancy, trauma, burns, and surgical operation [39].

Treatment

A medical trial for the therapy of HFRS the usage of ribavirin has been conducted. In this phase, ribavirin cure used to be check out in 242 patients with orthodox HFRS in China [41]. Morbidity and mortality had been each notably decreased authenticate efficacy when administered postexposure (i.e. prior to the onset of medical signs). In contrast, a scientific trial for the remedy of HFRS triggered with the aid of PUUV contamination performed in Russia indicated that intravenous ribavirin did now not alter viral load kinetics [42]. Two scientific trials for the cure of HPS the usage of ribavirin have been completed. Unfortunately, efficacy of intravenous ribavirin should now not be assessed in both of these trials. Similar survival curves have been determined in ribavirin-treated sufferers when in contrast to HPS sufferers at some stage in the identical timeframe [43]. Ribavirin therapy was once optimized the usage of the ANDV/hamster deadly HPS model. In one study, a hundred mg/kg and 50 mg/kg of ribavirin covered hamsters from deadly HPS besides toxicity. It was once additionally decided that ribavirin therapy beginning up to 14 days post-ANDV intranasal task resulted in good sized protection. In a 2d study, the postexposure efficacy of ribavirin therapy used to be validated with safety from deadly HPS disorder determined when ribavirin remedy started out three days following an intraperitoneal Andes virus (ANDV) mission [44,45]. No particular therapy for HCPS exists. Ribavirin, the solely authorized antiviral agent that is tremendous towards hantaviruses *in vitro* [46]. In 1999, HFRS applicant bare DNA vaccine was once developed with the aid of the subcloning method. The subcloned cDNA represented the small snippet (encoding nucleocapsid protein; S) or medium snippet (encoding G 1 and G two glycoprotein; M) of SEOV and was once duplicate into the impression vector WRG 7077. Syrian hamsters had been vaccinated with the S or M vaccine with a gene gun, and hantavirus-specific antibodies have been located in 5 of 5 hamsters or four of 5 hamsters, respectively. Evidence of contamination used to be monitored after venture with SEOV. 28 days later, hamsters vaccinated with M have been included hamsters from infection, however these inoculated with S had been now not covered [47]. In Chile ANDV is the unique etiological agent of HCPS with suggest annual incidence of 55 cases, 32% case fatality charge (CFR) and no precise treatment. Neutralizing antibody (NAb) titers at health facility admission correlate inversely with hantavirus cardiopulmonary syndrome severity. We designed an open trial to discover security and efficacy and evaluate pharmacokinetics of immune plasma as a cure approach for this disease [48]. A scientific find out about the use of intravenous ribavirin for treating Department of Defense personnel with hemorrhagic fever with renal syndrome (HFRS) obtained in Korea from 1987 to 2005 have been reviewed to decide the medical route of HFRS dealt with intravenous (IV) ribavirin [49]. Currently, no Food and Drug Administration ratify antiviral drug or immunotherapeutic agent is accessible for treatment of the hantavirus diseases. 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide has been proven to have *in vitro* endeavor and to some extent additionally *in vivo* exercise in opposition to some hantaviruses [50]. Studied the efficacy of ribavirin remedy given to HTNV-infected breastfeed mice on days 6 - 20 after infection. The ribavirin-treated mice had a greater survival price than the placebo manipulate group. Based on these findings, Huggins' crew performed a double-blind inactive drug controlled trial with HFRS sufferers in various nations along with China and Korea, displaying a sevenfold reduction in anguish in the ribavirin-treated team [51]. Newborn mice dealt with IFN-β earlier than contamination with HTNV, confirmed a survival charge of 85 - 90% in opposition to less than 20% for non-treated mice. The identical observations were described for PUUV and TULV. Human MxA protein, a kind I interferon-inducible intracytoplasmic protein, mediates antiviral moves towards a number of members of the Bunyaviridae household after interferon stimulation [52]. Tragacanthin polysaccharides from *Astragalus brachycentrus* and *Astragalus echidnaeformis* vegetation have been encourage as a manageable curative method to hantavirus disorganization as these compounds have been proven to have antiviral recreation towards Punta Toro virus (a phlebovirus member of the Bunyaviridae family, used as a model for surveying the cure of hantavirus infections) *in vitro* and *in vivo* [53].

Conclusion

Hantaviruses (HVs) are globally rising pathogens that can purpose diverse disorder syndromes worldwide. HV infections unfold to human beings from their herbal reservoirs, rodents. HV contamination can reason extreme ailments such as HV pulmonary syndrome or "HV cardiopulmonary syndrome" and "hemorrhagic fever with renal syndrome" in people via contact with contaminated rodents urine, feces, saliva, and blood droppings. Treatment is particularly supportive and will likely require intensive care unit monitoring, mechanical ventilation, and vasoactive agents. Aggressive fluid administration must be avoided due to the chance

of growing pulmonary edema and accelerating the development to respiratory failure. Extracorporeal membrane oxygenation may additionally amplify survival in extreme cases. Because no specific therapy, consisting of antivirals, has been proven to be positive for HCPS, emergency medical doctors ought to be vigilant for hantavirus exposures for the duration of the summer time and early fall months to facilitate time-sensitive prognosis and supportive care and alert the fantastic public fitness authorities.

Acknowledgment

None.

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