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Molecular characters of Hantaviruses, epidemiology and pathogenicity

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Abstract
The year 2020 has indeed been a year of crisis after the outbreak of Novel Corona virus there was another virus that showed its presence, it was Hantavirus. Several Chinese news channels reported death of a man due to hanta virus and the other 32 people were tested along, those who were in contact. There was indeed a risk of another outbreak while the whole world was still suffering from the COVID-19 crisis. Several novel Hantaviruses with unknown pathogenic potential have been identified in a variety of insectivore hosts. With the new hosts, new geographical distributions of Hantaviruses have also been discovered and several new species were found in Africa. Hantavirus infection in humans can result in two clinical syndromes: haemorrhagic fever with renal syndrome (HFRS) and Hantavirus cardiopulmonary syndrome (HCPS) caused by Old World and New World hantaviruses, respectively. This review focuses on the molecular properties of Hantaviruses that were found in the recent outbreaks, with a focus on epidemiology, the pathogenicity is described in relation to human as a host also diagnostic and possible treatment approaches have been described, microbiology remains a choice of interest as it is important to know complete structural components of the virus in order to tackle and block the lethal pathogenic abilities. The pathogenesis is likely to be a complex multifactorial process that includes contributions from immune responses, platelet dysfunction and the deregulation of endothelial cell barrier functions. This review summarizes recent data documenting interactions established by pathogenic Hantaviruses with their natural or human hosts that could highlight their different outcomes.

Keywords: hantavirus, epidemiology, HPS, HFRS, pathogenesis

Introduction
The hanta virus got its name from the name of river Hantan located in South Korea from where it was isolated. Hanta virus was found to cause Korean hemorrhagic fever isolated from the infected rodent field near Hantan river in the year 1978. After the Korean war (1950-1953) 3000 cases of Korean hemorrhagic fever were found among the united nation troops, further scientific studies with the electron microscope proved the identity of the virus as a new member of the family Bunyaviridae. Unlike the rest of the members of Bunyaviridae hanta virus did not had an arthropod vector and was capable of establishing an exclusive infection among the population of their specific rodent hosts. Considering hemorrhagic fever with renal syndrome a new genus was added in the family bunyaviridae in 1981. An outbreak in south-western united states that had peculiar symptoms of respiratory distress in infected patients proved the virus to be highly pathogenic. Examination of frozen lung tissue of the people who died of unexplained lung disease in the past led to the discovery of a new disease of the hanta virus that was named as hanta virus cardio pulmonary syndrome (HPS). Hanta viruses have co-evolved for millions of years along with their rodent and insectivore reservoirs. Rodent reservoirs include Cricetidae rodents (subfamilies Arvicolinae, Neotominae, and Sigmodontinae) and Muridae rodents (subfamily Murinae). Cricetidae rodents include lemmings of the northern hemisphere and new world mice and rats. (Mohammed A. Mir, 2010) [49].

Microbiology of Hanta Virus
Electron microscopic studies shows oval particulate nature of the virus having tripartite negative sense RNA, with a diameter of 80 to 210 nm (Johnson KM 2001, Schmaljohn CS,

1996) [28, 63]. The large segment genomic RNA is responsible for encoding viral RNA-dependent RNA polymerase (RdRp); the medium-sized (M) segment encodes viral glycoprotein precursor (GPC), the small (S) segment encodes the viral nucleocapsid protein (N). The lipid envelope has two glycoproteins, G1and G2. Like majority of the viruses both pathogenic and non-pathogenic hanta viruses envade the host cell by interacting between viral glycoproteins and cell surface integrin receptors. Human integrin αIIβ3 expressed by platelets, and αvβ3 expressed by endothelial cells, mediate the cellular entry for HFRS and HCP, causing hantaviruses (Gavrilovskaya IN *et al.*, 2008) [13]. Hanta viruses use clathrin-dependent endocytosis to enter a cell. Once inside three nucleocapsids are released in the cytoplasm along the viral RdRp. RdRp in turn initiates transcription and viral mRNAs are synthesized which encode three viral proteins.

Nucleocapsid Protein

Cells infected with hanta virus have this N protein in most abundant amount in cytoplasm. It takes 6 hours for the transcript to get detected in the infected cells.

Classification

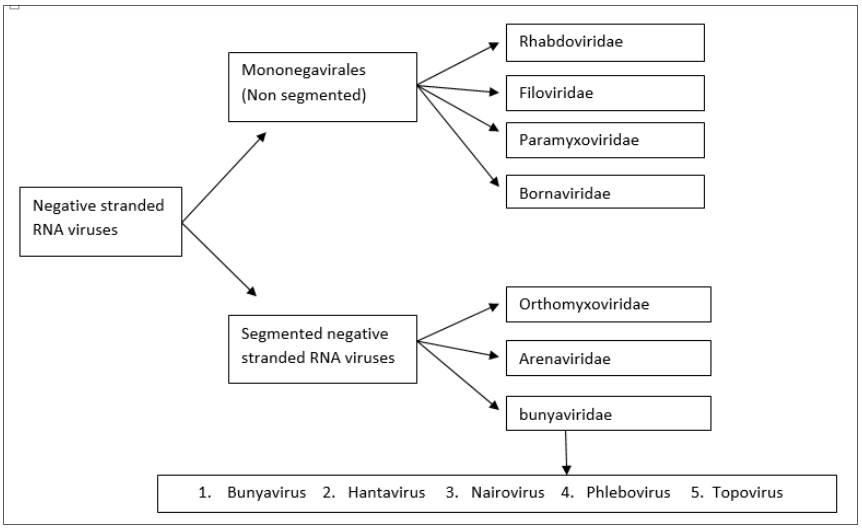

Fig 1: Microbiology of Hanta Virus

Functions

1. Encapsidation
2. Packaging of viral genome
3. A role in Initiation of transcription and translation of viral mRNA(Mir MA, *et al.* 2008, Mir MA, Panganiban AT, 2008) [47, 48]

Glycoproteins

The precursor for this is synthesized on ribosomes associated with Endoplasmic reticulum(ER) and then translocated to ER lumen by an endogenous signal peptide.

RdRp

Hantavirus RdRp protein is an uncharacterized protein with high molecular weight of 250 to 280 KDa. Functions-

1. Replicase activity.
2. Transcriptase activity.
3. Helix unwinding activities.

Epidemiology

Infection to man occurs via contact with aerosolized excreta or by direct contact with an infected rodent, on the other hand there are reports that claim the spread of ANDV (andes virus) from person to person (Enria D *et al.*, 1996, Padula PJ *et al.*, 1998) [6, 53]. The virus has ability to live in urine, saliva, feces (Hardestam, J., 2008) [18] and can live for weeks in the environment (Kallio, E.R., *et al.*, 2006) [31].

Majority of the cases are noticed in eastern Asia infected with hemorrhagic fever with renal syndrome (HFRS) caused by Old world hantaviruses Hemorrhagic fever with renal syndrome claims around 100,000 cases annually in China alone (Khan A, Khan AS, 2003). In Korea and eastern Russia more than 900 cases are observed infected with hemorrhagic fever with renal syndrome (HFRS) (Lee HW, 1989) [38]. Infection was detected in some insectivores like Suncus murinus (Tang Y.W, 1985) [70], Crocidura russula which is a shrew (Groen J. *et al.* 1995) [15], bats (Kim G.R. *et al.* 1994) [34], birds (Slonova R.A. *et al.*, 1992) [68] and domestic and wild cats(Luo Z.Z. 1985) [41]. There is no confirmation on the persistence of infection of these species and thus whether ther is a risk to man or not is not clear, while a Chinese study claimed risk of a cat ownership for acquiring infection (Xu Z.Y *et al.* 1987) [77]. Males of age 20 to50 years are most susceptible for hemorrhagic fever with renal syndrome, mortality depends on the type of virus (in general mortality is 0.1% to 10%). Majority of the patients are found in rural areas with thick rodent host population. Seoul virus (SEOV), a hantavirus causes disease in urban areas, this is because its host is domestic rat (Rattus norvegicus and Rattus rattus). Hantavirus pulmonary syndrome (HPS) cause by New world hantaviruses(SNV, ANDV, Monongahela virus, New York virus, Black Creek Canal virus, Bayou virus, Oran virus)has a mortality of 40%-50%. Korean hemorrhagic fever, epidemic hemorrhagic fever and nephropathia epidemic were old names for hemorrhagic fever with renal syndrome (Gajdusek DC *et al.*, 1987) [11]. In Korea among the united nation forces around 3200 cases came into notice of western physicians (1951-1954) (Gajdusek D 1962, Smadel J. 1953) [10, 69]. Other outbreak records that are believed to be due to hemorrhagic fever with renal syndrome were seen in Russia in 1913 and 1932, cases were seen in Manchuria in the troops of japan in 1932 (Gajdusek D 1962, Casals J. *et al.*, 1969) [10, 3] in Sweden (1934) (Zetterholm SG., 1934, Myhrman G., 1934) [81, 50].

Pathogenicity in relation to human host

As in some few human pathogens which are responsible for hemorrhagic fever, it was found that hantaviruses love to infect the endothelial cells thus making endothelial cells as a major target of infection. (Valbuena, G.; Walker, D.H, 2006) [74]. Hantaviruses cause a non-lytic infection, but the distorted endothelium results in hemorrhage, increased vascular permeability, acute thrombocytopenia and pulmonary edema or in some cases kidney failure.(Mackow, E.R., *et al.*, 2014) [44]. An immune response above the limits has tendency to impair barrier functions of the endothelium, this is a current hypothesis that explains vascular leakage (Hepojoki, J., *et al.*, 2014, Schonrich, G., *et al.*, 2015) [21, 65]. It is difficult to study the physiopathology in animal models as the infection in rodents remain asymptomatic more over there is a very narrow host specificity, one rodent species adapted to one rodent species. In a study a Turkish hamster was used as a rodent model for hantavirus disease (Hardcastle, K., *et al.*, 2016) [17]. In another study a Syrian hamster was used in which New World hantaviruses induced symptoms which were likely the same as in hantavirus cardiopulmonary syndromes(Ogg, M., *et al.*, 2013, Safronetz, D., *et al.* 2012) [51, 60]. Macaque non-human primate is a best animal model for both New world and Old world hantaviruses (Klingstrom, J., *et al.*, 2005, Safronetz, D, *et al.*, 2014, Sironen, T., *et al.*, 2008) [35, 61, 66]. An immune response above the limits has tendency to impair barrier functions of the endothelium, this is a current hypothesis that explains vascular leakage (Hepojoki, J., *et al.*, 2014, Schonrich, G., *et al.*, 2015) [21, 65]. Pathogenic hantaviruses are dangerous but they don't always cause severe diseases, there are some serological proofs obtained from investigation of human infections caused by hantavirus, that are considered to be non-pathogenic, like Prospect Hill (PHV) or Tula (TULV) viruses (Mertens, M., *et al.*, 2011, Yanagihara, R., *et al.*, 1984) [45, 78].

Increase in vascular permeability and acute thrombocytopenia are a main governing factors that drive the complete pathogenesis of hemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome (Mackow ER, Gavrilovskaya IN, 2009, Vapalahti O., 2001) [43, 75]. The replication for the virus occurs in vascular endothelium but it doesn't seem to cause direct cytopathic effects. (Kim S., *et al.*, 1993, Zaki SR., *et al.* 1995, Terajima M., *et al.*, 2007) [33, 37, 72]. They have a slow replication cycle, resulting in late viraemia on days 5 to 10 after infection (Terajima M., *et al.*, 1999) [73]. This suggests the virus persistence rather than the acute changes as seen in other haemorrhagic fevers (Mackow ER, Gavrilovskaya IN., 2009) [43]. An infected human kidney tissue exploration shows that the viral replication and immune response are involved in tissue injury (Terajima M., *et al.*, 2007, Temonen M., *et al.*, 1996) [72, 71]. In case a kidney gets infected the glomerular filtration decreases, Increase in glomerular permeability leads to substantial protienuria and so is a sign of tubular dysfunction. (Ala-Houhala I., *et al.*, 2002) [1]. Its not yet totally confirmed about the distribution of hantaviruses in the human body, after the virus enters the airway the infection starts when the Gn and Gc proteins present on the surface interact with the β-integrin receptors present on the cell membrane (Gavrilovskaya IN *et al.*, 1999, Gavrilovskaya IN, *et al.*, 2002) [12, 14]. The immature dendrite cells found near epithelial cells express β3-integrin receptors, they are believed to play a main role in dissemination of hantaviruses (Peebles Jr RS, Graham BS., 2001) [55]. They can also act as a means for transit of virions through the lymphatic vessels to regional lymph nodes, where the virions after replication can reach endothelial cells (Schonrich G., *et al.*, 2008) [64]. These cells don't hinder the replication but favour it, inducing immune activation specially by CD8+ T cells (Jonsson CB, 2010) [29]. Responses produced by immune system associated with the viral action produce inflammatory cytokine and chemokines which may be harmful, patients severely infected had elevated levels of interleukin-10 and tumour necrosis factor-α (Saksida A., *et al.*, 2011) [62]. The cytotoxic T cells add on to capillary damage in patients suffering from nephropathia epidemica through immunopathology, also by increased levels of nitric oxide and tumour necrosis factor-α. (Groeneveld PH., *et al.*, 1995, Linderholm M, *et al.*, 1996) [16, 15]. Hantavirus pathogenesis is a complex process which gets assistance from platelet dysfunction, immune responses and the dysfunction of endothelial cell barrier function.(Mackow ER, Gavrilovskaya IN., 2009) [43].

Differential diagnosis

Some conditions like pneumonia, sepsis with acute respiratory syndrome (ARDS), acute bacterial endocarditis can be confused with hanta virus cardio pulmonary syndrome. Other conditions like septicaemic plague, tularemia, histoplasmosis and coccidiomycosis were conditions that had presentations similar to HPS in southwest United States.

Diagnosis

Serological diagnostic approach includes detection of IgM and IgG antibodies in most patients, but also RNA is detected in sera during the first week of infection, typically the diagnosis is done based on specific IgM antibodies from a sample of serum, or alternatively by detecting viral RNA in blood, urine or saliva (Evander *et al.*, 2007; M¨ah¨onen *et al.*, 2007; Pettersson *et al.*, 2008; Plyusnin *et al.*, 1997a, 1999; Vapalahti *et al.*, 1996) [8, 56, 57, 58, 76]. Diagnostics from low IgG avidity of early samples has been done (Hedman *et al.*, 1991) [20]. luckily there is a working technique that is immunohistochemistry that can find the antigen of virus from samples obtained from the severally affected patients (Hautala *et al.*, 2002; Poljak and Avsic Zupanc, 1994; Zaki *et al.*, 1995) [19, 59, 37]. Enzyme immunoassays which are based on recombinant hantavirus N protein are being used by many laboratories and many commercial EIA tests are available (Elgh *et al.*, 1997; Sjolander *et al.*, 1997; Vapalahti *et al.*, 1996) [5, 67m, 76], in addition to this rapid immunochromatography test (Hujakka *et al.*, 2001a, 2001b, 2003) [24, 25, 26], strip immunoblot techniques (Figueiredo *et al.*, 2009; Hjelle *et al.*, 1997; Jenison *et al.*, 1994; Ksiazek *et al.*, 1995; Padula, 2000b) [9, 5, 27, 37, 54]. The serological cross-reactivity of anti-N response is can be used to diagnose the hantavirus infection, but for more deep detection/species distinction complicated tests like neutralization tests or assays that use truncated antigens with less conserved epitopes are used (Araki *et al.*, 2001; Koma *et al.*, 2012; Ogino *et al.*, 2003) [2, 36, 52].

Treatment

Supportive care is a given to patient including analgesics and antipyretics, sometimes symptoms are so severe that intensive care unit use becomes necessary. Fluid should be administered carefully due to risk of capillary leakage. Ribavirin has proved to be an angel drug in treatment, a controlled study showed the beneficial use of ribavirin

therapy in Hantan virus infection. It was observed that this therapy if initiated during first weeks of illness will reduce the death risk to seven times (Huggins *et al.*, 1991) [23]. Intravenous effects of Ribavirin have also been analysed for treatment of hantavirus cardiopulmonary syndrome, on the other hand there have been reports of no clinical benefits in a few limited trials (Chapman LE., *et al.*, 1999, Mertz GJ., *et al.*, 2004) [4, 46] Platelet transfusion becomes obligatory in case of substantial thrombocytopenia and bleeding (Jonsson CB., *et al.*, 2008, Linderholm M., *et al.* 2001, Enria DA., *et al.*, 2001) [30, 39, 7].

Conclusion

Hantaviruses have tendency to infect many as mentioned earlier, detection isn't easy in infected rodents thus there is a need to analyze the risk of being unhygienic at times when we eat and drink. Severely infected individuals should brought in sight of the health departments as soon as possible to avoid any risk of outbreak. Warnings issued by WHO should not be ignored. At times of an outbreak travelers returning to their native land should be quarantined. Early identification helps a lot in recovery. To raise awareness, clinicians should consult epidemiological data for guidance of the possible exposure, and be vigilant of patients presenting fever, myalgia, and thrombocytopenia.

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