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Hantavirus "Next In Line Of Biologic Warfare"

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Abstract

Over the past few decades understanding and recognition of Hantavirus infection has greatly improved worldwide, but both the amplitude and the magnitude of Hantavirus outbreaks have been increasing. With the new hosts, new geographical distributions of Hantaviruses have also been discovered and several new species were found in Africa. Hantaviruses (HVs) are globally emerging pathogens that can cause varied disease syndromes worldwide. HV infections spread to humans from their natural reservoirs, rodents. HV infection can cause severe diseases such as HV pulmonary syndrome or "HV Cardiopulmonary Syndrome" and "Hemorrhagic Fever with Renal Syndrome "in humans through contact with infected rodent's urine, faeces, saliva, and blood droppings. Many cases have been reported in India also since 1964. The main objective of this paper isto presents an overview of the HV infection, which can be an emerging global threat.

Keywords

Hantavirus infection; Global biologic threat; Hantavirus Pulmonary Syndrome; Hemorrhagic Fever with Renal Syndrome; Four Corners Disease.

Introduction

While the world is still grappling with the havoc wreaked by the highly infectious novel Coronavirus, another virus seems to be rearing its ugly head in China. Globally, emerging zoonotic pathogens remain a serious public health problem. In this regard, Hantaviruses have attracted a lot of attention as novel pathogenic serotypes. It has undoubtedly added to the fear and chaos among the people. However, the Centre for Disease Control and Prevention has said that the virus has very rare human-to-human spread[1, 2]. This paper intends to

present an overview of HV that may emerge as a global threat in future.

Hanta Virus

As per the Centre for Disease Control and Prevention (CDC), "Hantaviruses are a family of viruses spread mainly by rodents and can cause varied disease syndromes in people worldwide." It may cause Hantavirus Pulmonary Syndrome (HPS) and Hemorrhagic Fever with Renal Syndrome (HFRS).

This virus is known as the "New World" Hantaviruses in America and those known as "Old World" Hantaviruses are found mostly in Europe and Asia. Hantaviruses **(Genus Hantavirus, family Bunyaviridae)** are enveloped RNAviruses[3].

Historical Perspective

The first outbreak occurred during the Korean War (1950 to 1953)which is commonly referred to as Hemorrhagic Fever with Renal Syndrome (HFRS).The second outbreak of disease occurred in the Four Corners region of the United States(Arizona, New Mexico, Colorado and Utah) in 1993 and was initially referred to as **Four Corners disease**, which is now called Hantavirus Pulmonary Syndrome (HPS).

- 1951-1954: Hemorrhagic Fever with Renal Failure first recognized as a pathogen after an outbreak in Hantaankorea.
- 1977: disease isolated and named after Hantaan river.
- 1978: it was confirmed that the virus is carried by rodents.
- 1981: first successful propagation of virus in cell culture.
- 1993: outbreak of HPS in four corner regions of Colorado, New Mexico, Arizona and Utah.

Structure

Morphology

They are negative-sense, single-stranded RNA viruses with a three segmented genome. The vision displays round or pleomorphic morphology with a diameter of roughly 120-160 nm. The virus capsid is enveloped by a single layer envelope[4].The envelope surrounds three nucleocapsids and has surface projections. Surface projections are distinctive spikes which are surrounded by a prominent fringe embedded in a lipid bilayer that is 5 nm thick. These projections are 5-10 nm long and they produce a grid-like structure. Spikes protrude from the lipid bilayer envelope. Spikes consist of glycoprotein's Gn&Gc.Three segments:

- Large (L) codes for viral polymerase
- Medium (M) codes for G1 and G2 glycoprotein's
- Small (S) codes for nucleocapsid.

The capsid or nucleocapsid is elongated with helical symmetry. The ribonucleocapsid is filamentous and 200-300nm long, depending on the arrangement, and 2-2.5 nm wide.

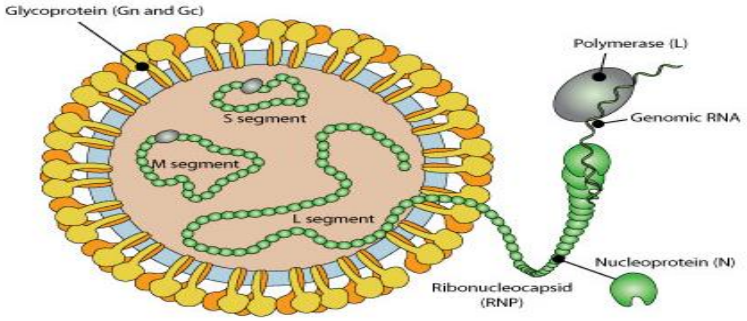

Fig. 1 - Structure of Hantavirus

Classification of Hantavirus

As of 2017, 41 species of Hantaviruses had officially accepted names, but there is ongoing debate about which viruses should be considered discrete species[5].Hantavirus species are recognized and they are divided into four distinct phylogroups:

FAMILY	SUBFAMILY	PRINICIPAL HOST
MURIDAE	Murinae	Old world rats &mice
CRICETIDAE	Arvicolinae	Voles & Lemmings

CRICETIDAE Sigmodontinae New world rats & mice CRICETIDAE Neotominae New world rats & mice

Pathogenic Hantaviruses, in nature carried by a specific rodent host species, can cause severe disease in humans with mortality rates from 12% (HFRS) to 40% (HCPS). Both diseases are acute febrile infections. HFRS is characterized by renal failure and haemorrhagic manifestations that vary from petechiae to severe internal bleeding. Pneumonia and cardio vasculardys function are characteristics of HCPS[6].

Epidemiology

- Hantan virus prototypical member of genus Hanta virus is the cause of a severe form HFRS endemic in Korea, China and Eastern Russia.
- Dobrava- Belgrade virus is an agent of Severe form of HFRS in the Balkans Greece and Russia.
- Seoul Virus is endemic in Asia, Europe and America.
- Puumala Virus is endemic in Europe and Scandinivea.
- Saaremaa virus – in Europe.
- Sin Nombre virus is the major cause of HPS in North America.
- Andes virus is the major cause of HPS in South America[7].
- Thottapalayam virus: The only known Hantavirus from India.

Pathogenesis and Life Cycle

Humans are infected by Hantavirus mainly through inhalation of aerosolized virus-contaminated rodent excreta and the higher the number of infected rodents, the higher the risk of human infection. Both the diseases result in defects in vascular permeability and platelet function. Human beta 3 integrins confer cellular susceptibility to HPS- and HFRS-causing Hantaviruses, a fact directly linking platelets, endothelial cells, and Hantavirus diseases to the use of cellular receptors that maintain capillary integrity and regulate platelet function[8].

The incubation period of Hantavirus is relatively long: 2–4 weeks. The very first barrier that the virus encounters when entering the body is the mucus gel that covers respiratory epithelial cells. In the lower respiratory tract, trapped microbes are removed by the ciliated cells that continually move the mucus with their cilia—away from the lungs to the throat. When the virus has passed the mucus gel, it encounters yet another barrier—the respiratory epithelium which has tight junction integrity and forms a particle-impermeable barrier and affects club cells. Despite being infected, these cells show no cytopathic effect (CPE) and the epithelial tight junction integrity is intact. The virus is able to infect via both the apical membrane and the basolateral membrane, and subsequently, virus particles are secreted bidirectional. Once the respiratory epithelium has been traversed, the

virus spreads to the lung endothelium and more distant locations in the body.

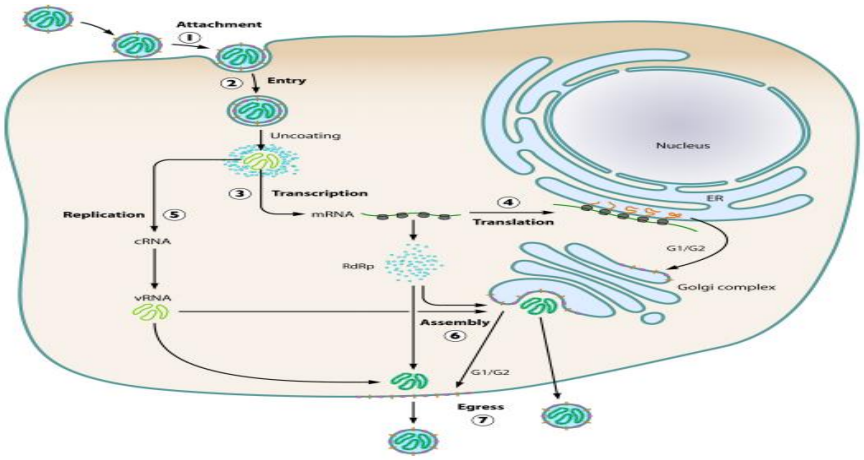

Fig. 2. The Hantavirus life cycle.

The basic steps include the attachment of the vision particle to the cell's surface through interactions between the host's cell surface receptors and the viral glycoprotein (1); entry through the use of receptor-mediated endocytosis and the uncoating and release of the viral genomes immediately thereafter (2); transcription of complementary RNA (cRNA) from the viral RNA (vRNA) genome using host-derived primers (3); translation of L, M, and S mRNAs into viral proteins using host machinery (4); replication and amplification of vRNA, assembly with the N protein, and transport to the Golgi apparatus (5); assembly of all components at the Golgi apparatus or, possibly for New World viruses, at the plasma membrane (alternative assembly) (6); and viral egress via the fusion of the Golgi vesicle harboring the mature virion particles with the plasma membrane (7).

Transmission

The viruses are excreted in urine, faeces, and saliva of infected reservoirs and it can stay infective in the environment for more than 10 days at room temperature, and even more if the temperatures are lower[9]. Most human infections occur when contaminated aerosolized rodent excreta are inhaled. Undoubtedly, the aerosol route of infection is the most common.

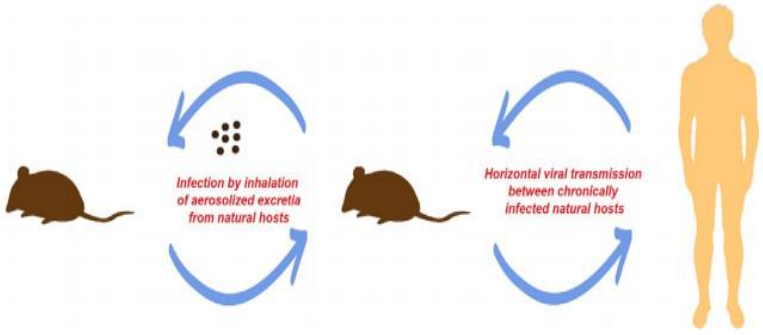

Fig.3. Hantavirus transmission route

CLINICAL SYNDROMES ASSOCIATEDWITH HANTA VIRUS

Hanta Virus Pulmonary Syndrome (HPS)

Early symptoms of HPS include

Fatigue

Fever

Muscle aches, especially in the thighs, hips, and back

Headaches

Dizziness

Nausea, vomiting, diarrhea or abdominal pain.

In the late stage of infection with a Hantavirus subtype, patients experience lung congestion, fluid accumulation in the lungs, and shortness of breath[10].

Hemorrhagic Fever with Renal Syndrome (HFRS)

Initial symptoms begin suddenly and include intense headaches, back and abdominal pain, fever, chills, nausea, and blurred vision.

Individuals may have flushing of the face, inflammation or redness of the eyes, or a rash.

Later symptoms can include low blood pressure, acute shock, vascular leakage, and acute kidney failure, which can cause severe fluid overload.

The severity of the disease varies depending upon the virus causing the infection[10].

Laboratory Diagnosis of Hantavirus

A positive serological test result, evidence of viral antigen in tissue by immune histochemistry, or the presence of amplifiable viral RNA sequences in blood or tissue, with compatible history of HPS, is considered diagnostic for HPS[10].

1. Direct detection- a. Microscopy.
   b. Antigen detection.
   c. Nucleic acid detection.
2. Virus isolation.
3. Serologic tests.
4. Identification– a. Serologic methods.
   b. Genetic methods.
5. Typing Systems-- Sequence analysis.

Hantavirus Research In India

Almost four decades later, in 2005, the first hospital-based study on Hantavirus infections in India was reported and suggested that Hantaviruses may cause symptomatic and asymptomatic infections. Commercial laboratory assays, ELISA and IFA were employed for diagnosis. The second hospital-based study on Hantavirus infections defined serological evidence of Hantavirus infections as seropositivity for Ig M (by ELISA and IFA) and Ig G (by ELISA and IFA) in acute samples [2]. TPMV (THOTTAPALAYAM VIRUS) was believed to be an arbovirus till it was characterised as a hantavirus by its ultra structural features. Among the hantaviruses, TPMV is the only one that does not show cross-neutralisation with other serotypes. The presence of TPMV Ig G antibodies in the patient gives the impression that TPMV may be a human pathogen and S. murinus its natural rodent host.

Treatment of Hantavirus

- Supportive therapy is the mainstay of care for patients with Hantavirus infections.
- Care includes careful management of the patient's fluid (hydration) and electrolyte (e.g., sodium, potassium, chloride) levels, maintenance of correct oxygen and blood pressure levels, and appropriate treatment of any secondary infections.
- Dialysis may be required to correct severe fluid overload[11].
- Drugs can be administered as either a post exposure prophylactic or a therapeutic measure.

Candidate Drug	Drug Type	Date of Last Publication
Ribavirin	Nucleoside analog	2017
Lactoferrin	Iron-binding protein	2001
ETAR	Nucleoside analog	2008
Favipiravir	Pyrazine derivative	2013
Vandetanib	Tyrosine kinase inhibitor	2016
Methylprednisone	Corticosteroids	2013
JL16, MIB22	Monoclonal antibodies	2018
Human convalescent plasma	Polyclonal antibodies	2015
Purified human plasma from transchromosomal bovine	Polyclonal antibodies	2014

Table 1: Candidate drugs evaluated in Hantavirus animal models

Prevention and Control

The prevention of diseases caused by Hantaviruses is based on principles of rodent control such as reducing rodent shelter and food sources in and around the home, eliminating rodents inside the home and preventing them from entering the home, using standard precautions for preventing Hantavirus infection.

In addition to minimizing the risk of hantavirus exposure, the prevention of Hanta viral disease could be augmented by effective vaccines and strategic vaccination of at-risk populations. No WHO approved vaccines are available. But, inactivated vaccines have been developed in Asia & used locally in Korea for protection of humans against HFRS[11].These vaccines are prepared from brains of suckling rats/mice or from cell cultures infected with Hantaan virus/ seoulvirus----**Hantavax**, commercially produced in S. Korea.

STRATAGIES for development of new Hanta virus vaccines include:

1. Recombinant nonpathogenic viruses,
2. Rodent/ cell culture derived inactivated virus.
3. Naked DNA

4 .E. Coli expressed truncated nucleocapsid as an immunogen.

Vaccination of individuals in areas of endemicity or those who could be exposed to the virus in military, clinical, and research settings may offer a strategy for reducing the risk and incidence of disease.

Conclusion

Hantaviruses have a widespread geographical distribution. The absence of detailed studies on Hantaviruses in India is due to many reasons, such as the absence of diagnostic kits which even if available, are exorbitantly priced and the lack of awareness among clinicians. Future research based on the present work includes characterization of the circulating species, extensive study of possible rodent reservoirs in India and development of more cost-effective and user-friendly diagnostic tools (serological and molecular) for rapid diagnosis of Hantavirus infections in humans.The best way to combat HV infection is to minimize contact with rodents at home, workplace and by taking all the precautions to reduce possible exposure to potentially rodent infectious materials, as prevention is better than cure.

References

1. Clement J, Maes P, Lagrou K, Van Ranst M, Lameire N. A unifying hypothesis and a single name for a

complex globally emerging infection: Hantavirus disease. Eur J Clin Microbiol Infect Dis 2012; 31:1-5.

2. AvšičŽupanc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect 2016.
3. Nichol ST, Spiropoulou C, Morzunov S, RollinPE, Ksiazek TG, Feldmann H, Sanchez A, Childs J, Zaki S , Peters CJ, 1993. Genetic identification of a Hantavirus associated withan outbreak of acute respiratory illness. Science 262: 914-917.
4. Kaukinen P, Vaheri A, Plyusnin A. Hantavirus nucleocapsid protein: A multifunctional molecule with both housekeeping and ambassadorial duties. Arch Virol 2005; 150: 1693-713.
5. Vaheri, A., Strandin, T., Hepojoki, J. et al. Uncovering the mysteries of Hantavirus infections. Nat Rev Microbiol 11, 539–550 (2013).
6. Chandy S, Mathai D. Globally emerging hantaviruses: An overview.Indian J Med Microbiol 2017;35:165-75.
7. Jonsson CB, Figueiredo LT, Vapalahti O. A global perspective on Hantavirusecology, epidemiology, and disease. Clin Microbiol Rev 2010; 23:412–41.
8. Linderholm M, Elgh F. Clinical characteristics of hantavirus infections on the Eurasian continent. Curr Top MicrobiolImmunol 2001; 256:135-51.
9. Kallio ER, Klingstrom J, Gustafsson E, et al. Prolonged survival of Puumala hantavirus outside the host: evidence for indirect transmission via the environment. J Gen Virol 2006; 87:212734.
10. Elgh F, Lundkvist A, Alexeyev OA, et al. Serological diagnosis of hantavirus infections by an enzyme-linked immunosorbent assay based on detection of immunoglobulin G and M responses to recombinant nucleocapsid proteins of five viral serotypes. J Clin Microbiol 1997; 35:1122-30.
11. Brocato, R.L.; Hooper, J.W. Progress on the Prevention and Treatment of Hantavirus Disease. Viruses 2019, 11, 610.