

HISTORY OF HANTAVIRUS

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Abstract

Hantavirus is an expanding group of virus species. It can cause various clinical manifestations mainly categorised as: hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. It belongs to the family bunyaviridae that gets transmitted through rodents, bats and several insectivores species. There are various species which are getting discovered on a regular basis. There are various immune responses noticed due to the intervention of hantavirus in a host There are various commercial vaccines found against hantavirus, in which HANTAVAX - korean commercial vaccine. Further the traces and history of the hantavirus infections in various geographic locations are discussed. So this review aims to study the history of hantavirus, its structural and functional aspects, its effect over the world, public health is discussed and spread awareness about the same.

Keywords: *hantavirus; history; disease; epidemiology; hosts; prevention.*

Introduction

Hantavirus is large group of viruses .In humans, cases vary based on severity from mild to severe .Fatality rate due to these viruses are generally 30% and above [1].Species mainly affected are rodents like Norway rats, black rats, south American mouse genera, deer mice it also affects Insectivores- Like shrews , moles, along with others, specifically Gaeta mouse shrew , Asian musk shrew. Other animal hosts are nonhuman primates- cats, dogs, orangutans, chipmunks, many more [2]. Hantavirus belongs to genus Hantavirus, large family Bunyviridae with 300viruses. It Infects animals, plants, humans, and arthropods. Old world and new world hantaviruses are type main categories of hantavirus based on geographical distribution of rodents and type of illness caused. though, both share the same nucleic sequences and similar life cycle.[3]. China has a history of Hantaan virus infected striped field mouse cases.in Russia, there were cases reported due to Hantaan, Puumala,

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Khabarovsk viruses. Worldwide, there were cases due to Seoul infected Norway rats. In India there were cases of Thottapalayam virus infected musk shrew and Many more [4]. The incubation period of these hantaviruses are averagely 1 to 5 weeks. Early symptoms of these viral infections are fever, fatigue, myalgia, muscle aches, headaches, dizziness. on further prolongment Diffuse pulmonary edema, Dipsea, crackles, hypoxia, hypotension. This further causes low blood pressure, bleeding under skin and finally kidney dysfunction which leads to death in the case of hemorrhagic fever with renal failure while respiratory discomforts gradually leading to cardiovascular shocks happen in hantavirus pulmonary syndrome conditions. These Coagulation abnormalities, cardiopulmonary conditions may occur to be fatal.[5]

Hantavirus distribution in east and central Africa were cases with ulu guru virus infected mouse shrews, and many others. Serotypes of hantavirus were bats, rodents, shrews which kept expanding the boundaries of the host [6]. Bat borne hantavirus were seen mostly in forestlands, scrubs regions. Shrew borne hantavirus were recorded in forestland, savanna regions. Rodent borne hantavirus were mainly found in forestland regions. Human sero prevalence is found in forestland, savanna, grassland areas[7]. Hantavirus distributions in Asia are mainly Lymphocytic Choriomeningitis Virus [LCMV] and mostly infect rodents and insectivores. New cases are found in hosts on ranges of shrews.[8] Hantavirus was known and believed to be dangerous to the health of bats but not to humans which got changed when Hantaviruses caused some human diseases by underrecognized pathogenic agents in the south Asian region. Changing climates, increased globalization, altered land use makes tends to turn habitats to have more rodent species and other host species susceptible to hantavirus which increases human risk by the zoonotic viruses.[9]

More than 24 pathogenic hantaviruses are prone to infect humans, worldwide. Diseases are classified as two major divisions which are hemorrhagic fever with renal failure[HFRS] [HFRS] and hantavirus pulmonary syndrome [HPS].[10] Hemorrhagic Fever Renal Syndrome are mainly found in Europe, Asia, Africa whereas HPS is found in America. Hantavirus is one of the emerging zoonotic pathogens where infections spread fast for the past decade. Yet, Many cases are left undiagnosed [11]. Hantavirus outbreak was seen in Panama in 1999-2000 which affected Los Santos, Herrera, Veraguas, Coclé provinces. Reservoirs of these viruses are sylvatic rats, rodent species. Environmental, ecological factors are seasonal impacts in disease trends. India is the origin of the most divergent hantavirus-[Thottapalayam thottimvirus] TPMV. [12].But there is no detailed study in India due to absence of diagnostic kits which are exorbitantly costly, lack of awareness in clinicians. New world hantaviruses are considered as bioterror weapons, Zoonotic pathogens which were left unnoticed until the four-corner outbreak in 1993.Mild infections due to these hantaviruses are often left unnoticed.[13] Future studies should be done with user-friendly tools for rapid diagnosis, study over the rodent reservoir, more cost-effective diagnostic tools, awareness should be spread about the same.[14]

TAXONOMY

Hantavirus genus has an expanding group of species which belongs to the family bunyaviridae, like murine borne viruses, arvicoline borne diseases, neotaminae- borne viruses, etc. there has been new discovery of about 14 new virus species in the past decade, mostly of socio morph mammals infected ones. There are many molecular methods done to identify new virus species to accurately determine the biological and geographical distribution of the viruses and its host in this world[15]. The genus hantavirus has 36 recognised species in 2019.

GENOME

Family bunyaviridae predominantly has four genera: *Loanvirus*, *Mobatvirus*, *Thottimvirus*, and *Ortho Hantavirus*. It is a negative sense RNA genome virus with 3 fragments, namely large, middle and small segments. It encodes mainly four proteins – viral polymerase, viral surface glycoproteins and nucleocapsid proteins[16].RNA dependent RNA polymerase is the enzyme used for transcription and replication. There are no non-structural proteins found unlike the other genus of this family.

LIFE CYCLE

There are various steps involved in the life cycle of hantavirus. First, the virus attaches to the cell surface through alpha-v-beta-3 by endocytosis or micropinocytosis, then there is uncoating of the viral genome and transcription of complementary RNA to the viral DNA , which forms the 3 segments of the virus which gets

replicated more. ; there is production of the viral proteins which is transported with the help of Golgi apparatus[17] in which the virions are secreted away through exocytosis.

MAJOR OUTBREAKS

During 1982 ,Dr. Wang Lee and his colleagues found an etiological agent responsible for hemorrhagic fever with unique renal complications from an infected wild rodent species, *apodemus agrarius* which is commonly found in northern and eastern Asia. [18] In future it was named hantaan as it was first isolated from an infected rodent near Hantan river, South Korea. These cases have a history of scientific approaches which point to similar clinical complications when more than 3000 US troops faced korean hemorrhagic fever during Korean world war[1951- 1953][19]. These troops had renal shock and failures in which 30% of them suffered further hemorrhagic complications with a mortality rate more than 10%. [20]

Then there were similar cases found in europe and scandinavia commonly known as Nephropathia Epidemica. It was milder than HFRS but had severe future complications like gastrointestinal hemorrhage which lead to more fatal cases.[21] The virus was isolated in cultured human cell lines which showed a shared etiology with all these outbreaks which proved that this virus was responsible for HFRS type of illness for the past 140 years including the world wars. [22]

There was evolution of human pulmonary syndrome which had a massive outbreak in 1993 at southwestern United States. On analysis, tests and various diagnoses these infections was found to share the etiology of hantavirus which had already affected nearly 21 states, left unrecognised. It was called an HPS outbreak in four corner regions of the USA [1993- 1994]. It was mainly transmitted through deer mice which had a quite large population due to heavy rainfall conditions at four corner regions where New Mexico, Colorado, Arizona and Utah intersect [23].

EPIDEMIOLOGY

ASIAN SPECIFIC COUNTRIES - CHINA

HFRS is considered to be a class B disease which causes a great risk to public health. About 30 provinces out of 32 provinces are infected by HFRS disease. 9 provinces have a large incident rate of about 80%. China alone accounts for 40-50% of HFRS disease all along the world. Recently , there was a case filed in march 2020 which was further reported as spread to 32 other people.

RUSSIA

First case was recorded in 1934, by 1995 there were 3145 cases found. The viral infection showed similarity to that of Korea and China. [24]. This place is mainly infected by Puumala and Dobrava hantavirus. Puumala causes mild symptoms whereas dobrava exhibits its severe form.

KOREA

Korea is the area where hantavirus was first isolated. About 300-400 cases are recorded annually with a death rate contributing 1%. 35.6% of the population infected were farmers which occurred mostly in the month of October, November, December.[25] Here , hemorrhagic fever with renal syndrome is infected by hantaan, seoul and puumala hantavirus.

JAPAN

There have been no cases reported in japan for the past few decades. Though there are no new cases , the repeated survey has revealed that the place is mainly infected by Vladivostok and Amur virus.

THAILAND VIETNAM SINGAPORE

There are less HFRS cases referred to with the symptoms of this disease, whereas there are many cases with fever of unknown origin with serological evidence of hantavirus infection.

INDONESIA

There were hantavirus infections during the dengue outbreak.[26]. In the past 35 years, the seroprevalence in rodents is said to be 35% whereas in humans it's 15%. These viruses have been studied here in animals and humans since 1984.

INDIA SRILANKA

There have been many cases reported with the correlation between leptospirosis and hantavirus infection. But there are so many cases with fever of unknown origin but diagnosed with positive results of hantavirus antibody. There should be more diagnostic tools and technology to diagnose more cases in India. There has been Asian house shrew borne thottapalayam hantavirus infection [27]

EUROPE

Puumala virus is detected in Europe, mainly in British Isles, southern Mediterranean areas, and northernmost tundra regions. Tula virus is seen in Central and Western Europe. Saaremaa virus infects striped field mice seen in Estonia, Russia, Finland, Germany, Denmark, Slovakia.

HFRS is a common disease found in most European countries like Finland, northern Sweden, France, Belgium, Germany, Balkans and part of European Russia. Epidemiological data is not available for some areas like Greece, Ukraine, Poland, UK.[28].

AFRICA

The first case was reported in 1984. There are hantavirus antibodies found in hosts like rodents, humans, etc. in areas like Egypt, Guinea, Djibouti, Nigeria and Senegal. In 2010, a novel hantavirus was discovered in Africa which causes HFRS.

AMERICA

The infections started with an acute respiratory disease outbreak during four corner regions of the USA in 1993. Out of 30 pathogenic hantavirus species, 15 are reported to be present around America [29].

TRANSMISSION

Hantavirus is a bunyavirus transmitted through rodent species, bats and insectivores. Initially, it was believed that hosts had no actual disease due to the virus, but then it was discovered there would be risk in the hosts survival, characteristic changes in the hosts infected tissue. Slowly the virus and host relation evolved within various ranges of species which brings in more chance of a pandemic outbreak with new virus species evolving putting public health in danger[30]. The infection is spread through the contact of bodily fluids of the infected rodent species, particularly from saliva, urine and feces. This transmission is the same for both the disease caused.

DISEASE CAUSED

The diseases due to these infections are mainly haemorrhagic fever with renal syndrome [HFRS] and hantavirus pulmonary syndrome [HPS], based on which the group of viruses is divided as old world and new world hantaviruses respectively. The main characteristics of these diseases increases vascular permeability, hypotension, thrombocytopenia, leukocytosis. But there is no treatment for these infections.[31]. There also exists virus species which do not cause either of the illness such as Prospect Hill ortho hantavirus. HFRS causes

symptoms after an incubation period of 2-4 weeks like fever, backaches, abdominal pains, nausea. Further it causes low blood pressure, bleeding under skin and finally kidney dysfunction which leads to death.[32]. This illness is caused by hantavirus in Asia and Europe. The mild form of this illness in Europe is called “nephropathia epidemica”.

HPS shows an incubation period of 16 to 24 days. Initially it shows mild and vaguely specific symptoms due to fluid build up in the lungs. Then severe symptoms occur which leads to cardiovascular shocks [27]. This illness is caused by virus species in America which is typically associated with new world hantavirus though puumala hantavirus causes these symptoms in Europe.

IMMUNE RESPONSE

Innate immune response

There is an innate immune response in the pathogen infected host cells, which is suppressed by the hantavirus to some extent. There is an activation of interferons and action of inducible proteins is slowed down by the virus. There is an elevation of the antigen presenting cells, natural killer cells secrete cytokines which proceeds slowly by the presence of hantavirus. All the mechanism invades the virus infected tissues, trying to respond to the viral infection. [33]

Humoral immune response

The IgG mostly abundant antibody, efficient against the hantavirus infections, directs to the viral protein in the disease conditions.[17] Mostly all the patients have at least M class anti-virus antibodies. Neutralisation test is the widely used diagnosis for these infections. It is believed that there exists a strong relation between the antibody neutralization titer and the severity of the infection.

PREVENTION

VACCINES

There are various vaccines developed from the killed virus and recombinant DNA technology. Mostly the inactive killed virus is derived from the infected rodent’s brain. These vaccines work similar to that of the rabies vaccines.[34] The main successful commercial Korean invented vaccines – HANTAVAX, proved efficient against the rodent and human infections. As of 2020, there are no US FDA approved vaccines against hantavirus. But there are bivalent species vaccines against hantavirus and seoul virus in China and Korea. Apart from these further four types of vaccines have been developed.

ANTIVIRAL THERAPY

There is no proper therapeutic treatment invented to cure this infection. Ribavirin drug has to some extent showed antiviral activity against the hantavirus increasing the survival rate [35]. Persons infected with hantavirus infections are admitted in hospital with proper ventilation to support their respiratory distress. Immunotherapy, antibodies neutralisation treatments are provided.

CONCLUSION

Hantavirus is an expanding group of virus species with severe clinical manifestations. Though there are various diagnostic methods, the diagnosis is limited due to its affordability and availability. Thus mostly these cases are left undiagnosed and treated which increase its mortality rate. Proper vaccinations and preventions should be done in places susceptible to this infection to prevent its outbreak. Further studies should focus on the different diagnostic tools and proper treatment to these infections with wide availability and feasible affordability for better efficiency. The symptoms, severity and its vaccinations, precautions should be discussed and awareness should be spread about the same.

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CONFLICT OF INTEREST

The author declares that there was no conflict of interest.

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