Hantavirus Conducted Route from Mice to Human: Potential Dangers and Outcomes of Zoonosis

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Abstract

The hantavirus is associated with deadly illnesses including hemorrhagic fever associated with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS), and there are an astounding 200,000 new infections of this virus per year. It is a major concern for world health. Murid rats are the major hosts of these viruses, which operate as silent reservoirs that enable zoonotic transmission to humans via aerosolized faeces. Particularly in endemic regions, the intricate interplay between environmental conditions and human behaviour substantially impacts the transmission of hantavirus infections. This research addresses the complicated biology and pathophysiology of hantaviruses, underlining the crucial need for better immunisation and treatment alternatives. Although numerous promising vaccine candidates are being researched, problems remain in obtaining enduring protection and assuring safety. Also, efforts into neutralizing antigens as prospective therapies give a glimmer of light to better the lives of patients. A comprehensive approach that involves monitoring, public education, and research into innovative vaccines and therapies is required to battle hantavirus infections, decrease public health hazards, and protect vulnerable populations.

Keywords: Hantaviruses, Rising Infectious Diseases, Zoonotic Transmission, Pathogenesis, Immunization Techniques

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Introduction

1.1 History

Hantaviruses are a serious worldwide health issue, resulting in around 200,000 fatalities yearly (Bi et al., 2008). The entire variety of disorders is steadily rising internationally (Watson et al., 2014). Two significant Hantavirus outbreaks have drawn worldwide attention in the recent century. The initial HFRS epidemic occurred somewhere during the Korean War (1950–1953), affecting around three thousand US military personnel (Tian & Stennis, 2019).

In 1993, the southern United States saw its second HPS pandemic. They appear to be most infectious in their natural host populations, where they cause persistent viral infections and regularly reduce rodent excretion. They cause two severe febrile illnesses in human beings: hemorrhagic fever associated with renal syndrome (HFRS) and Hantavirus pulmonary syndrome (HPS) (Khaiboullina et al., 2005).

1.2 Biology

Three families of Hantaviruses were identified: the Orthohantavirus genus, the Hantaviridae family, and the Bunyavirales order. As shown in Figure 1 (Mittler et al., 2019), three-terminus assemblage of single-stranded, negative-strand molecule of RNA makes up the genomes of Hantaviruses (Avšič-Županc et al., 2019). According to the length of their nucleotide sequence, these genomic regions are classified as short (S), medium (M), or large (L) in stages. Encapsulated viruses with a diameter of 80–120 nm are known as Hantaviruses.

The envelope membrane is formed by an external lipid bilayer that is produced by the Golgi complex. About 10 nm long spikes (viral proteins) emerge from the lipid bilayer. Such spikes have a remarkable reactivity for oligomers and are heterodimers of the glycoproteins Gn and Gc (Huiskonen et al., 2010). It is believed that the spikes' complex and unusual structure is unique to encapsulated viruses (Huiskonen et al., 2010).

The N protein, which is essential for the development of the viral nucleocapsid, is encoded by the 1,700–2,100 nucleotides that make up the S phase. The 1,150 amino acid lymph protein of the glycoprotein is encoded by the M phase, which is made up of 3,613–3,707 nucleotides. The cell peptidase complex uses the continuous pentapeptide motif "WASA" at its the N-terminal as an objective point for translating degradation (Löber et al. 2001). The L-phase of a virus facilitates protein synthesis and genome replication, while mutations in the M and S segments can

alter the virus's virulence and immunogenicity (Du et al., 2014). This kind of virus may become inactive, like other enveloped viruses, when exposed to detergents, ultraviolet (UV) radiation, hypo chlorine solutions, natural solvents, and high temperatures (60°C for 30 minutes).

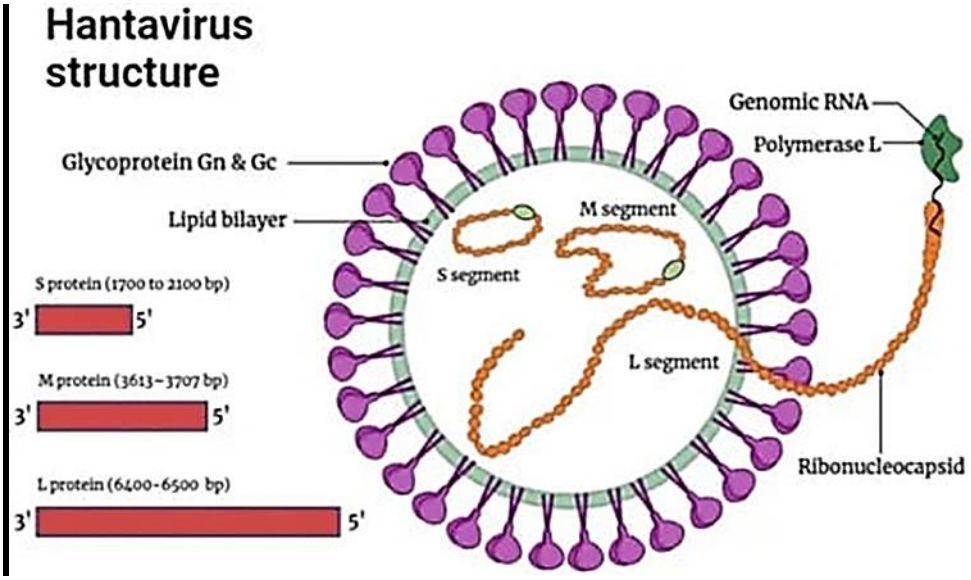

Fig. 1: Hantavirus structure and genome organization (Image generated: www.biorender.com).

1.3. Host Range

Murid rats are the principal reservoir of Hantavirus infection. Over a lengthy period of time, the virus and host have co-evolved, and infected rats no longer suffer hantavirus-related illness (Ulrich et al., 2003). Contrary to the initial assumption that a single rodent species has emerged as the most common host for a single hantavirus species, current evidence indicates that there may be two rodent hosts for each virus species, as well as multiple viruses in a single host species (Nemirov et al., 2002; Scharninghausen et al., 2004; Weidmann et al., 2005). Additionally, several investigations have revealed Hantavirus infection in species other than rats, including agricultural animals, moose, cats, and dogs. Still, it is questionable if these animals are accidentally bloated or have grown prominent as supplementary herbivore reserves (Zeier et al., 2005).

The spread of unmarried Hantavirus species is connected to their global dispersion in hosts, and genotypes from the same area are typically associated (Plyusnin, 2002; Zeier et al., 2005). Humans are not the main host of Hantaviruses, thus infection occurs via inadvertent contact with virus-containing, aerosolized rodent excretions such as urine, feces, or saliva. People who handle or live near diseased rodents are more likely to be infected, and assessments generally demonstrate that the percentage of seropositive persons in such agencies is greater than in those acting as controls (Zöller et al., 1995; Deutz et al., 2003).

2. Prevalence

Hantaviruses may also cause severe and deadly diseases, such as nephropathy epidemica (NE) in Europe, hemorrhagic fever associated with renal syndrome (HFRS) in Asia, and Hantavirus associated with cardiopulmonary syndrome (HCPS) in North and South America. Hantaviruses have killed 1–15% of individuals with HFRS, 0.1–1% of persons with NE, and 40–60% of those with HCP in the last decade, with 200,000 people worldwide contracting them every 12 months (Bi et al., 2008; Singh et al., 2022).

3. Life Cycle of Hantaviruses Disease

A total of 48 possible Hantavirus species have been linked with moderate, lifetime chronic infections in rodents on practically every continent except Australia and Antarctica (Forbes et al., 2018). Host changes are being observed in all flora and fauna, in addition to rodent mammalian hosts, corroborating the idea of genetic variety and co-evolution (Bowen et al., 2001). Also, environmental conditions play a crucial role in keeping Hantavirus infections out of the doors of reservoir hosts, with cold and damp environments contributing to protracted infections (Jonsson et al., 2010). As a consequence, host chronic illnesses guarantee that viral transmission happens inside the environment via rodent waste and urine. Continuous transmission of the virus, coupled with favorable external environmental circumstances, permits Hantaviruses to stay throughout the environment. Hantavirus particles from the surrounding reach host cells by breathing.

As seen in Figure 2, Hantavirus infects its host by binding the viral glycoprotein to cellular surface receptors on lymphocyte cells, follicular dendritic cells, macrophage cells, epithelial cells and endothelial cells (Jonsson et al., 2010). The kidneys and the lungs are among the vascular endothelial cells and macrophages that the Hantavirus primarily targets. Numerous experiments have demonstrated that the virus's Gn protein would enhance binding by interacting with integrin receptors in the cell's outer layer (Mir and Panganiban, 2010). Alpha and beta chains are both present in integrins, a form of heterodimeric protein. This enables interaction between cells and the extracellular matrix (Takagi & Springer, 2002; Campbell & Humphries, 2011). After binding, the virion is eventually moved to the lysosome through pits coated with clathrin.

Viruses spontaneously freed from the endolysosomal compartment released 3 viral nucleocapsids in the cytoplasm (Jin et al., 2002). Clathrin-coated cell membranes produce clathrin-coated vesicles (CCVs), which encircle the virus (Ramanathan and Jonsson, 2008). Three mRNAs are produced by the RdRp, one from each of the viral RNA's stages (S, M, and L). Free ribosomes translate the mRNAs that S and L

create. The translation of M-specific mRNAs into proteins occurs in the rough endoplasmic reticulum (RER). The internal cleavage of the glycoprotein precursors in the remarkably conserved amino acid sequence of Gn and Gc results in the production of the glycoproteins (Spiropoulou, 2001). Figure 3 shows how the glycoproteins Gn and Gc are transported to the Golgi complex for glycosylation, where hantaviruses were designed to appear. The process of exocytosis is followed by translocation to the Golgi cisternae, followed by exocytosis to escape to the secretory vesicle's outer membrane. But nothing is known about the complexities of virion egress (Szabo, 2017). Additional viral entry points include micropinocytosis, clathrin-independent endocytosis-receptor-mediated, caveola, macropinocytosis, LDL and cholesterol-mediated endocytosis (Ramanathan et al., 2007).

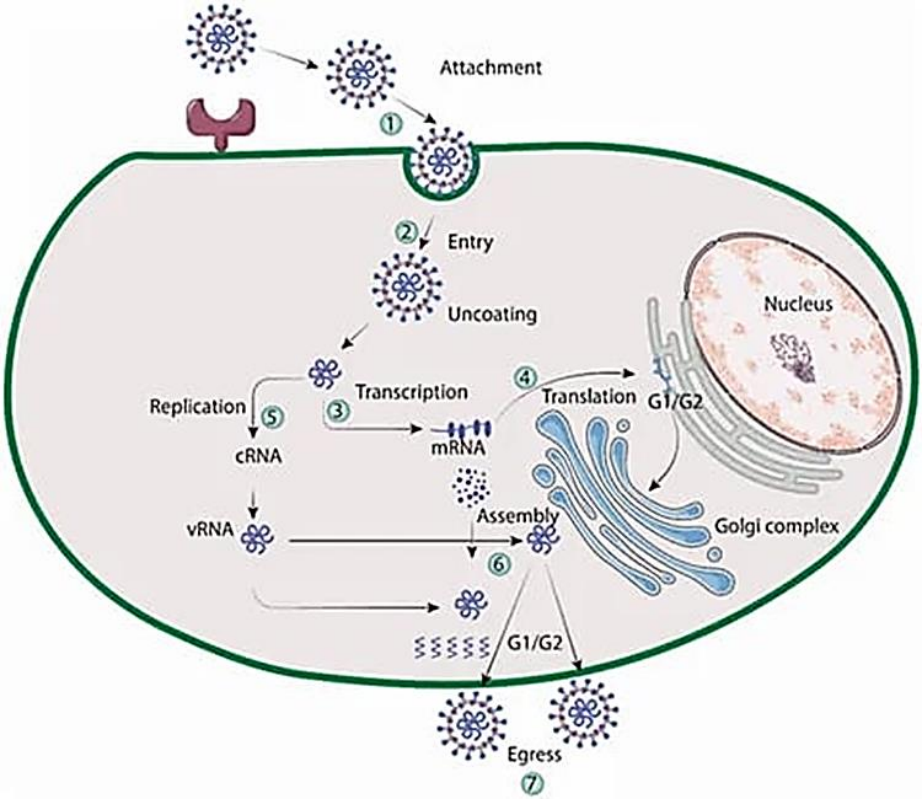

Fig. 2: Replication cycle of Hantavirus (Image generated: www.biorender.com).

4. Pathogenesis of Hantavirus

HPS inside the lung is induced by Gn and Gc surface glycoproteins that bind with β3 integrin receptors on endothelial cells, macrophages, and platelets (Jonsson et al., 2010; Ermonval et al., 2016; Munir et al., 2021). The pathophysiology of Hantavirus is complicated. This contact begins a cascade of immunological responses that impair vascular permeability, ending in pulmonary edema, respiratory failure, hypotension, and cardiogenic shock. Macrophages identify Hantavirus and produce proinflammatory cytokines such as TNF-, IL-1, and IL-6 (Jonsson et al., 2010; Ermonval et al., 2016; Munir et al., 2021). After antigen identification, CD4 T cells develop into helper cell types: Th1 and Th2. Th1 cells release IFN-γ and TNF-β, which contribute to cell-mediated immunity. IL-12 governs this differentiation (Jonsson et al., 2010). IL-4 and IL-5, which are released by Th2 cells, stimulate humoral and allergic reactions. Inducible regulatory T cells play a crucial role in regulating immunological responses and infection-induced disease by releasing immunosuppressive cytokines such IL-10 and TGF-β (Jonsson et al., 2010).

The processes driving HFRS development are also connected to increased vascular permeability. However, efficient retailers infiltrate endothelial cells without creating cytopathic repercussions (Jonsson et al., 2010). The animal versions for ANDV and HPS that were developed for Syrian hamsters are no longer applicable to HFRS, and there is no appropriate animal version for HFRS. When exposed to wild-type PUUV strains, cynomolgus monkeys that are no longer used to a mobile lifestyle exhibit signs of NE-like contamination and diagnostic diseases, such as elevated levels of C-reactive protein, cytokines (IL-10, IL-6, and TNF-) and nitric oxide (Jonsson et al., 2010). Fatigue, fever, muscular pains, malaise, disorientation, chills, nausea, vomiting, diarrhea, and stomach discomfort are early signs of Hantavirus infection (CDC, 2016). The preceding symptoms are frequent and may be connected with a variety of disorders. Cough and shortness of breath are late warning indications of HPS, however typical clinical indicators of HFRS and HPS include fever, myalgia, thrombocytopenia, leukocytosis, and, for more severe patients, capillary leak syndrome linked with hypoxia (Jonsson et al., 2010).

5. Diagnosis

Monitoring for symptoms of HCPS, HFRS, and NE may benefit in early diagnosis. Since Hantaviruses are transmitted by rodents, doctors can utilize the patient's medical history to determine if the patient has visited rat-infested areas or has come into contact with rats or their droppings. A peripheral smear and a complete blood count (CBC) are examples of diagnostic tests (Dvorscak & Czuchlewski, 2014). Hantavirus is currently identified by cell culture, serological screening, and molecular diagnostics (Munir et al., 2021). Serological tests for IgM and IgG in acute symptomatic HFRS and HPS are reliable owing to the overabundance of N protein antibodies.

One such test is the indirect immunofluorescence assay (IFA), which is less often conducted since it needs the identification of virus-infected cells. Apart from IFA, the most widely used serology tests for Hantaviruses include IgM capture ELISAs, immunoblot assays (IBA), cognizance reduction neutralization (FRNT), and indirect IgG and IgM immunosorbent assays using enzymes (ELISAs) (Munir et al., 2021). Also, fast IgM capture ELISA is equally effective in the diagnosis of HFRS and HPS. Furthermore, the knowledge of the viral genome has led to breakthroughs in highly sensitive diagnostic techniques.

The whole hantavirus genome may be swiftly identified by reverse transcription-PCR (RT-PCR) utilising blood, serum, or organ tissue samples as early as the first day of sickness (Munir et al., 2021). Nestled-RT-PCR methods, which use primers designed for conserved sections with excessive homology in the small, medium, and large segments, may also be required for low amounts of viral RNA in human and rat tissue samples (Munir et al., 2021). Hantavirus RNA has been revealed to be active in infected mice, leading to nested-RT-PCR testing of the Hantavirus genus. Pan-hantavirus primers were utilised to identify Hantavirus in African wood mice from Guinea (Munir et al., 2021).

6. Treatment

Currently, the United States Food and Drug Administration has not authorised any antiviral medications for the treatment of HFRS (Hantavirus Hemorrhagic Fever with Renal Syndrome) or HPS (Hantavirus Pulmonary Syndrome). As a consequence, the strategy to coping with severe instances is centred primarily on passing over emotional support. Maintaining appropriate hydration and electrolyte balance in these individuals is critical. HFRS patients who have experienced substantial renal loss may need extracorporeal blood purification, including dialysis. On the other hand, HCPS patients may further need ventilatory assistance or extracorporeal membrane oxygenation. (Munir et al. 2021). The absence of FDA-approved medicines or vaccinations is the number one hurdle to adequately controlling this dangerous pathogen. In addition to supportive care, alternative therapeutics include antivirals, DNA-based vaccinations, and polyclonal and monoclonal antibodies are preferred. Such approaches have showed success in neutralizing Hantavirus and are being explored as possible therapies for Hantavirus illness (Munir et al. 2021).

Human ANDV immune plasma delivered systemically seems to be safe for HCPS (Vial et al., 2015). In my view, employing mAb JL16 or MIB22 as single-agent therapy or combining both in a drink might be a powerful treatment for patients with ANDV-precipitated HCPS. Small animal models have revealed that numerous DNA vaccines, together with passive transfer of polyclonal serum from rabbits, ducks, and human assets, may protect against HCPS. High levels of hantavirus-specific immunoglobulin G (IgG) in HCPS patients early in the course of the illness imply survival. Furthermore, injection of adult immunological plasma from HCPS survivors to severe HCPS patients dramatically decreased mortality. This implies that antibodies may effectively suppress Hantavirus in vivo (Garrido et al. 2018).

7. Preventing Human Infection and Disease

Assessing the influence of climate change on human Hantavirus outbreaks may guide future comprehensive response plans. However, integrated rodent management methods seem to be a more practical way to reducing human illness in the medium term (Zhang et al. 2010). Focusing on endemic and endemic regions may be an early and cost-effective strategy. Strict rodent management in and around ports, ships, and shipping containers may also assist minimise SEOV transmission (Lin et al., 2012). This is crucial because international product mobility, especially via delivery, may contribute to the spread of this hantavirus, since its rodent host (R. norvegicus) has not been demonstrated to display large-scale movement patterns on its own (Gardner-Santana et al., 2009).

Educating the public on suitable rodent control practices seems to be especially crucial. The usage of mousetraps will enhance the risk of infection, presumably as a consequence of interaction with the lure (Vapalahti et al., 2010). As a consequence, public health professionals may be hesitant to employ rat traps. Also, a growing corpus of research on human risk factors for contamination gives a list of high-risk behaviors for which preventative steps should be implemented. Both handling of wood and disinfection of limited spaces should be done in a well-ventilated atmosphere, preferably with a face mask to prevent breathing in virus-carrying debris. Additionally, outside walls and seasonal residences should be completely aired before entering. In dangerous foreign regions, avoiding living in immaculate environs may also prevent people from exposure to rat feaces.

Prevention is especially crucial for jobs with high exposure hazards, such as farmers, forest workers, and army. Wearing a face mask during severe physical activity and/or dust exposure may also lower the risk of respiratory exposure. Vaccination of these people may be suitable in endemic locations, but additional work is required to confirm the effectiveness of such treatment approaches. Although no Hantavirus vaccine is presently certified by the Food and Drug Administration (US) or the European Medicines Agency (EMA), inactivated virus vaccines have been deployed (Zhang et al., 2010). Concerns regarding immune-mediated reactions to trace quantities of rat antigens have impeded approval in Europe and the United States, despite the fact that four out of five human vaccines are manufactured from rodent cell cultures (Schmaljohn, 2009). Molecular vaccines and DNA injections based exclusively on viral expression vectors provide the potential of a future universally allowed immunisation (Hooper et al., 2001; Custer et al., 2003). Finally, a greater knowledge of the processes by which domestic animals transmit Hantaviruses to people is required. If the findings of such research are robust, screening and/or immunisation of domestic animals may be an effective way to limit the danger of Hantaviruses to people. However, there is yet insufficient knowledge to advocate such steps.

Conclusion

A major global health concern, Hantavirus causes 200,000 new infections year and can cause severe outcomes such pulmonary syndrome and a hemorrhaging fever with renal syndrome. The virus mostly affects murid rats, which can spread it to people through their urine, saliva, and rodent droppings. Researchers are working to develop viable vaccines and treatment alternatives to help healthcare systems and prevent future outbreaks. Collaboration between scientists and public health organizations is necessary to address the complexity of the virus and ensure improved community protection and prevention measures. It is possible to reduce Hantavirus infections and safeguard susceptible groups by improving research, public awareness campaigns, and surveillance. Using state-of-the-art technologies to monitor illnesses in

humans and wildlife can help detect potential epidemics, and raising public knowledge of the disease's progress can help protect people and communities. Research on Hantavirus ecology, transmission factors, and vaccination efficacy must continue. A multimodal approach that integrates observing, education, and research can protect vulnerable populations against Hantavirus infections, including older adults, those with pre-existing medical conditions, and those residing in remote areas.

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