Seoul Virus: Clinical Picture and Treatment

14

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ABSTRACT

Seoul virus is a Hantavirus that caught the public attention initially during Korean war (1950-1953) and has an association with rodent populations and human health. A concise overview, exploring the various aspects of Seoul virus including its viral characteristics, epidemiology, ecology, pathology, clinical features, diagnostic criteria and treatment along with prevention has been provided. Seoul virus has a prevalence in urban environments where the brown rat (Rattus norvegicus) serves as reservoirs. Human are exposed to this virus through inhalation of contaminated aerosols pr direct contact with rodent excreta. Clinical manifestations of Seoul virus are discussed in detail ranging from asymptomatic cases to severe conditions described as Hemorrhagic fever with Renal syndrome (HFRS) and Hantavirus Cardiopulmonary syndrome (HCPS). The features associated with HFRS are fever, nausea, vomiting, headache, backache, petechiae and internal bleeding. The patient may go into shock. Pneumonia, cardiogenic shock and pulmonary oedema are associated with HCPS. The diagnosis of Seoul viruses is done by ELISA, serological tests, hemagglutination test and IFT. The treatment is only providing symptomatic care and supportive along with monitoring of vitals. There is currently no approved specific medical therapy available. Strategies for rodent control and prevention of human infections include the role of public health initiatives, education and community engagement. In conclusion, a comprehensive exploration of Seoul virus, bridging gap between epidemiology, ecology, pathology, clinical aspects, diagnostic and preventive measures have been provided in this chapter.

Keywords: Seoul virus, Hantavirus, Rodents, HFRS, HCPS, ELISA test, Prevention.

CITATION

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1. INTRODUCTION

The disease resembling hantavirus infection, which was originally mentioned in Chinese writings 900 years ago, initially caught the public attention during the Korean War (1950–1953). Korean hemorrhagic fever, also known as hemorrhagic fever with renal syndrome (HFRS), struck more than 3000 United Nations personnel. Cause of disease remained unclear until Lee et al. (1978) reported on Hanta virus (HTNV) which was found in lungs of the virus' natural reservoir, the striped field mouse (Apodemus agrarius) (Lee et al. 1978; Brummer-Korvenkontio et al. 1980; Nichol et al. 1993; Vapalahti et al. 2003; Heyman et al. 2009). Severe illness can be induced by pathogenic hantaviruses having fatality rates ranging from 12% (HFRS) (Heyman et al. 2009) to 40% (HCPS) (MacNeil et al. 2011). In nature, these viruses are carried by a particular rodent host species. Both illnesses are acute febrile infections that are typically contracted by inhaling dust or aerosols infected with rodent excreta or viruses (Jonsson et al. 2010). Renal failure and various haemorrhagic symptoms, from petechiae to severe internal bleeding, are characteristics of HFRS. Cardiovascular dysfunction and pneumonia are HCPS features. A typical result of hantavirus infection appears to be increased permeability of the microvascular endothelium (Klempa 2009). There are currently around 28 hantaviruses known to infect humans and cause conditions including pulmonary oedema, severe hemorrhagic conditions and acute renal failure.

2. VIRAL CHARACTERISTICS

All of viruses that cause HFRS are members of the Hantavirus genus of Bunyaviridae family. Hantaviruses are enveloped particles having a diameter of 90–120 nm. The genome is divided into medium, large and tiny segments. A nucleocapsid protein along with large protein and two glycoproteins are coded by these segments.

Arthropods including ticks, sandflies, and mosquitoes are responsible for spreading the majority of the Bunyaviridae family's viruses to humans. On the other hand, rodents propagate all hantaviruses and they are transmitted to humans through rodent urine, saliva, and feces aerosol. Also, they are transmitted from rodents to rodents by the same mechanism. Although the vast majority of evidences militate against ectoparasites' role in virus transmission, the matter is not entirely resolved. Since the Hanta virus was first discovered in a field mouse, Apodemus agrarius in Korea, an increasing number of novel but related viruses were discovered in various rodent species, as well as infrequently in acutely unwell humans. The results of serology employing the neutralization test (NT), monoclonal antibodies and indirect immunofluorescence test (IFT) have been used to classify these novel viruses. The hantaviruses were initially split into four distinct families or serotypes by these findings (Niklasson and Le Duc 1984). The genus of the primary rodent host and the serological grouping is is the same. Apodemus rodents are the source of the first serotype (Hantaan virus), Rattus rodents are the source of second serotype (Seoul virus), serotype 3 is composed of isolates from Clethrionomys (Puumala virus), and serotype 4 is referred to the isolates from Microtus (Baek et al. 1988). A belt from Norway in the west to Sweden, Finland, the Soviet Union, China, and Korea to Japan in the east is where HFRS is endemic. Throughout this belt, there is variation in the clinical severity of HFRS. In Asia, there is a severe variant (KttF) with major hemorrhagic signs and mortality, while in Europe, there is a milder type (nephropathia epidemica) that has minimal hemorrhagic manifestations. This type is of little to low lethality (Lee 1982). Both types of the disease were found in the former Soviet Union. Given that several cases of Korean Hemorrhagic Fever have been identified in eastern European nations like Greece and Yugoslavia, for example, the line between a serious disease and a benign condition is not quite clear-cut. Asia has recorded cases of clinical sickness brought on by the Seoul virus, commonly known as the urban rat virus. Both serologically and clinically, Hantaan virus infection is closely connected to Seoul virus disease. In contrast to patients infected with the Hantaan virus, the patients suffering from Seoul-

related viruses have lower mortality rate. The taxonomy of Bunyaviridae family members divides these viruses into genera and different viruses based on serology, such as NT (Bishop et al. 1980).

3. EPIDEMIOLOGY

In the majority of the world's regions, hantavirus antibodies have been discovered in humans and rodents (Leduc et al. 1986). However, only cases of patients who were clinically unwell have been documented from Europe and Asia. The number of cases that are fatal in Korea each year ranges between 300 and 900 and the fatality rates that were estimated previously was at 7 to 15%. Mortality rate has decreased to 5% over the past ten years due to better and efficient medical care (Lee 1982). The incidence rate in China has grown recently (perhaps as a result of better surveillance) and in 1982, 60,000 cases were reported with 5% fatality rate. There have been up to 168 cases per 100,000 population recorded annually in highly endemic regions of China (Song et al. 1984). The most endemic districts of Sweden have documented an incidence rate of 30 per 100,000 residents during such peaks, which happen every 3–4 years. Infection occurs year-round in areas of far eastern Asian locations but the peak incidences are reported in hot summers (May to July) and in mild winters (October to December). The bulk of occurrences in Scandinavia and the European Soviet Union region happen from October to April. there are up to 30% of people of older age groups who have antibodies, as has been reported in Sweden. This means that the case-to-infection ratio may be around one to ten (1:10). The majority of clinical cases are men of working age. The male to female sex ratio exceeds up to 2:1 in many places (Niklasson and LeDuc 1987). Farmers and woodworkers, soldiers and hunters are among the groups that are most frequently affected. A common perception is that there is low prevalence in children as compared to adults. All HFRS survivors are believed to recover without long-term effects, however some patients have been noted to have chronic hypertension and persistent renal impairment. According to renal biopsies tests, GFR and renal function tests, the prognosis of nephropathia epidemica is good. Within 3 months' majority of the patients slowly restore their renal function. In Some patients, it may take a prolonged time of up to 8 months for renal impairment (Settergren et al. 1990). People who work with artificially and sometimes naturally infected laboratory rodents have had a number of laboratory infections. In a Moscow institute, 113 lab employees were affected by an outbreak in 1961. Finland reported making similar findings. Hantaan virus transmission attempts to laboratory rats were followed by an outbreak in Seoul (Settergren et al. 1990).

4. ECOLOGY

Hantaviruses, in contrast to other Bunyaviruses, do not spread through arthropod vectors but rather through persistently infected rodent or insectivore hosts including bats as well (Fig. 1). The ecology of hantavirus and their geographic dissemination are correlated with dispersion of their natural habitat. In 1976, Apodemus agrarius, a field mouse was the first mammal which the HTNV (a hantavirus prototype strain) was isolated from (Lee et al. 1978). When the HFRS etiological agent was first discovered in South Korea, research studies were conducted worldwide that resulted in additional new HFRS-associated viruses to be recognized. Hence, it has been recorded that hantaviruses are able to spread not just across the Europe and Asia but also in the Americas and Africa.

It is generally acknowledged that spontaneous host infection is undetectable and does not result in disease. Although this is the case, some researches have shown various detrimental effects of hantavirus infection on survival of hosts. Gradual growth of infected animals and the existence of histological alterations in infected tissues were also recorded. The virus and host co-evolved, hantaviruses are usually closely connected to a single rodent species (Ahlm et al. 2000). Other animal infections include those of

moose, red fox, domestic cats and dogs are regarded as a spillover with a negligible or zero risk of human infection. The diverse biogeographic and anthropogenic stresses on the environment appear to be a major cause of spillover infections of sympatric hosts, however, since many cases of this phenomenon have been reported and this is also dangerous for public health as excessive infection promotes natural reassortment and the creation of new species of hantavirus (Plyusnin and Morzunov 2001).

5. PATHOGENESIS

Despite the presence of viral antigen in different organs, viral infections mostly affect renal or pulmonary endothelial cells and macrophages in both humans and animals (Hughes et al. 1993). Animals, in contrast to humans, frequently carry the virus throughout their lifetimes and are still capable of spreading it to other animals and people. As a result, our knowledge of viral pathogenesis has been constrained by the absence of obvious disease in the natural host (Mackow and Gavrilovskaya 2001). As the Syrian hamster model is utilized for ANDV and HCPS, therefore, it is not appropriate for HFRS and there had never been an animal model for HFRS. Increased vascular permeability, acute thrombocytopenia, and significant microvascular bed permeability are the main pathophysiologic events in both HFRS and HCPS (Vapalahti et al. 2003). The vascular endothelium is where hantavirus replication takes place,

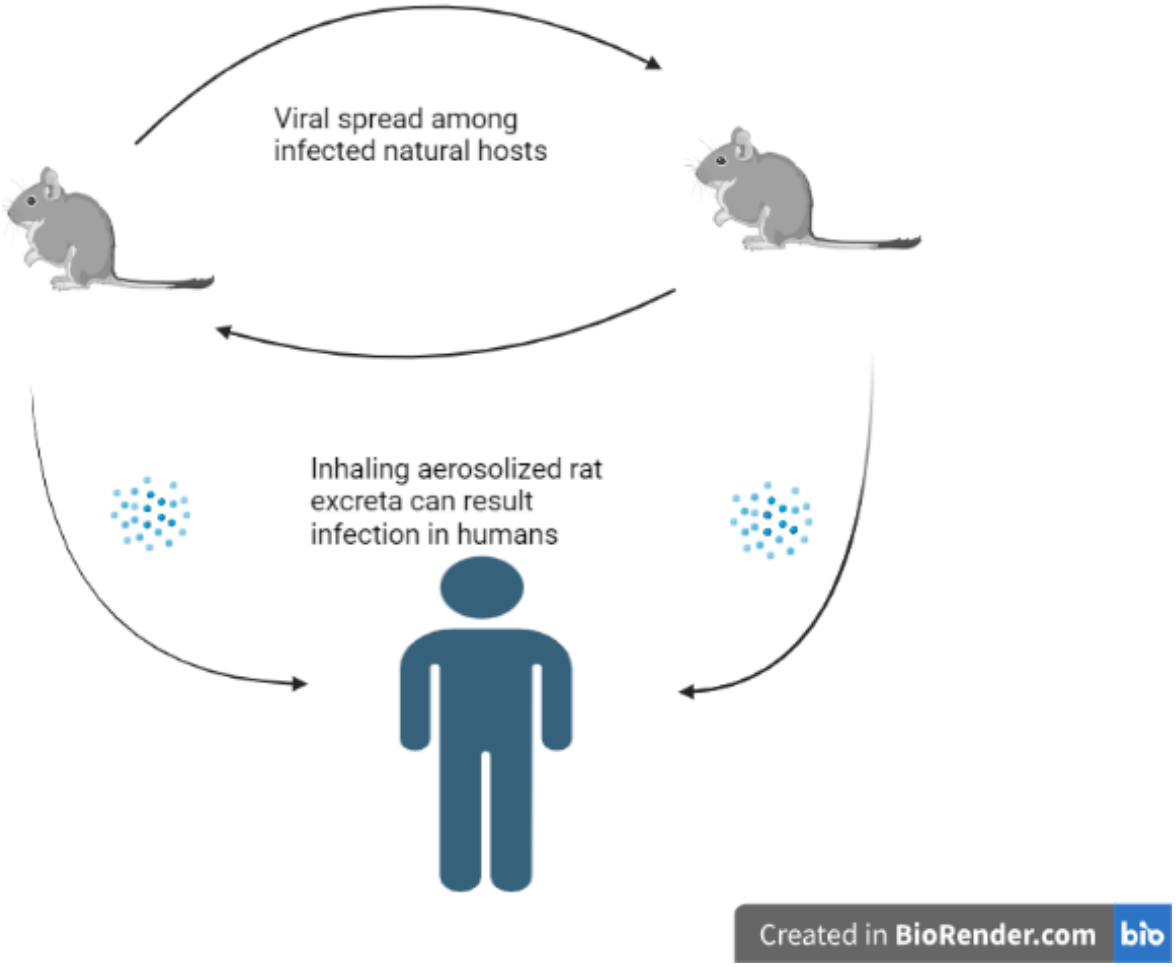

Fig. 1: Spillover infection to humans.

However, it doesn't appear to have a direct cytopathic effect. Since the virus replication cycle is very sluggish and late sepsis develops 5 to 10 days after infection (Terajima et al. 1999). This suggests that the virus persists rather than progressing in an acute lytic manner like other viral hemorrhagic fevers do. The viral antigen was found in the human kidney tissues of NE patients combined with inflammatory cell infiltrations and tubular damage, pointing to the possibility that immune response and viral replication are both implicated in tissue harm. The primary location of enhanced expression of numerous cytokines and the adhesion of endothelial molecules detected is the peritubular region of the distal nephron (Temonen et al. 1996). In acute NE, the renal involvement is characterized by significantly reduced renal plasma flow and glomerular filtration rate. Massive proteinuria is caused by increased glomerular permeability, which is a symptom of tubular dysfunction (Ala-Houhala et al. 2002). After the inhalation of infected aerosols, at first there is a communication of surface proteins with integrin receptors on the membranes of target cells. The exact mechanism by which virus spread throughout the human body is yet unknown. It has been demonstrated that human endothelium cells can be infected by pathogenic which includes SEOV, HTNV, PUUV, SNV as well as non-pathogenic hantaviruses which includes Tula virus, Prospect Hill virus. However, they do so using various integrin receptors (αvβ1 versus α5 β3) (Gavrilovskaya et al. 1999). Given that they express 3-integrin receptors and are found close to epithelial cells, immature dendritic cells likely play a crucial role in viral spread (Peebles and Graham 2001). They are also capable of acting as carriers to deliver the virus through lymphatic ducts to local lymph nodes from where they can further travel to endothelial cells after undergoing further replication (Schönrich et al. 2008). Virus replication is permitted by these cells particularly in the macrophages and CD8+ T cells which triggers immunological activation. It has been demonstrated that pathogenic hantavirus-infected cells exhibit increased viral titers due to a delayed type I interferon response (Schönrich et al. 2008). Antiviral innate immune responses can create inflammatory cytokines and chemokines, which can be a double-edged sword. Patients with both DOBV and PUUV infections had higher serum levels of interferon, interleukin-10, and TNF. Additionally, the patients suffering from more severe clinical condition of the disease had considerably high levels of TNF and interleukin-10 (Saksida et al. 2011). Interleukin-6 and tumor necrosis factor levels are increased in NE patients, although transforming growth factor-1 levels are low, indicating a milder type of the disease. In late stages of an acute infection, the overexpression of converting growth factor-1 points to a beneficial immunoregulatory function (Sadeghi et al. 2011). Cytotoxic T cells may cause capillary damage in NE patients by immunopathology, as well as through elevated levels of nitric oxide and tumor necrosis factor (Groeneveld et al. 1995; Linderholm et al. 1997). Hantaviruses, as opposed to other viruses that can cause haemorrhagic fever, cause the maturation of infected dendritic cells which results in a potent T-cell response during acute infection (Kilpatrick et al. 2004). The cytotoxic T-lymphocyte response, which coincides with the development of clinical illness in NE patients, increased the number of activated CD8+ T cells and reversed the CD4+ versus CD8+ T-cell ratio (Chen and Yang 1990; Kilpatrick et al. 2004). The negative impact of the immune response in HFRS-infected individuals is caused by the immune response of T helper type 1 and T helper type 2, proinflammatory cytokines in higher levels and inadequate regulation of them by their regulatory cytokines (Schönrich et al. 2008). Platelet dysfunction, immune responses and the dysregulation of endothelial cell function are all thought to play a role in the complicated multifactorial pathogenesis of the hantavirus. Above that, it was demonstrated that a genetic susceptibility to severe HFRS disease was correlated with HLA type, although different hantaviruses were linked to various HLA haplotypes. It has been demonstrated that the HLA-B8 DRB103:02 haplotype is particularly related with a genetic susceptibility to a more harsh form of HFRS that is brought on by PUUV (Mäkelä et al. 2002). Following ANDV infection, the same HLA haplotype was once more associated with a severe course of HCPS (Ferrer et al. 2007). Additionally, HLA-B*35 was more frequently found in individuals with severe illness development from DOBV infection, notably in cases where the patient died. The same HLA type has

previously been linked to a severe form of HCPS brought on by SNV (Korva et al. 2011). Fig. 2 shows the increase vascular permeability in response to viral infection.

6. CLINICAL PICTURE

Humans infected with hantaviruses may develop one of two clinical conditions, HFRS or HCPS, depending on whether the virus is from the Old World or the New World. Because separated capillary beds—renal medulla capillaries in HFRS and pulmonary capillaries in HCPS—are predominately damaged, the hantavirus-associated illnesses differ from one another. However, all hantavirus infections begin with identical first symptoms, such as a rapid onset of high fever, malaise, myalgia and other flu-like symptoms. Increased vascular permeability causing hypotension, thrombocytopenia, and leucocytosis with a left shift are additional common variables of HFRS and HCPS (Khaiboullina et al. 2005).

7. HAEMORRHAGIC FEVER WITH RENAL SYNDROME

The severity of the clinical signs and symptoms of HFRS may vary from asymptomatic to mild to moderate to severe and depends on the disease's etiological agent. Generally speaking, HFRS brought on by HTNV, Amur/Soochong virus, or DOBV are more severe and have fatality rates ranging from 5 to 15%, whilst SEOV produces intermediate disease and PUUV and SAAV bring on mild disease with mortality rates of less than 1%. However, a single PUUV infection case could be severe, a single HTNV infection could be mild, and infections are typically associated with subclinical seroconversion (Linderholm and Elgh 2001; Vaheri et al. 2013). The five unique phases of a typical course of HFRS are febrile, hypotensive, oliguric, polyuric, and convalescent. The illness begins suddenly with a high fever, chills, headache, backache, abdominal pains, nausea, and vomiting after an incubation period

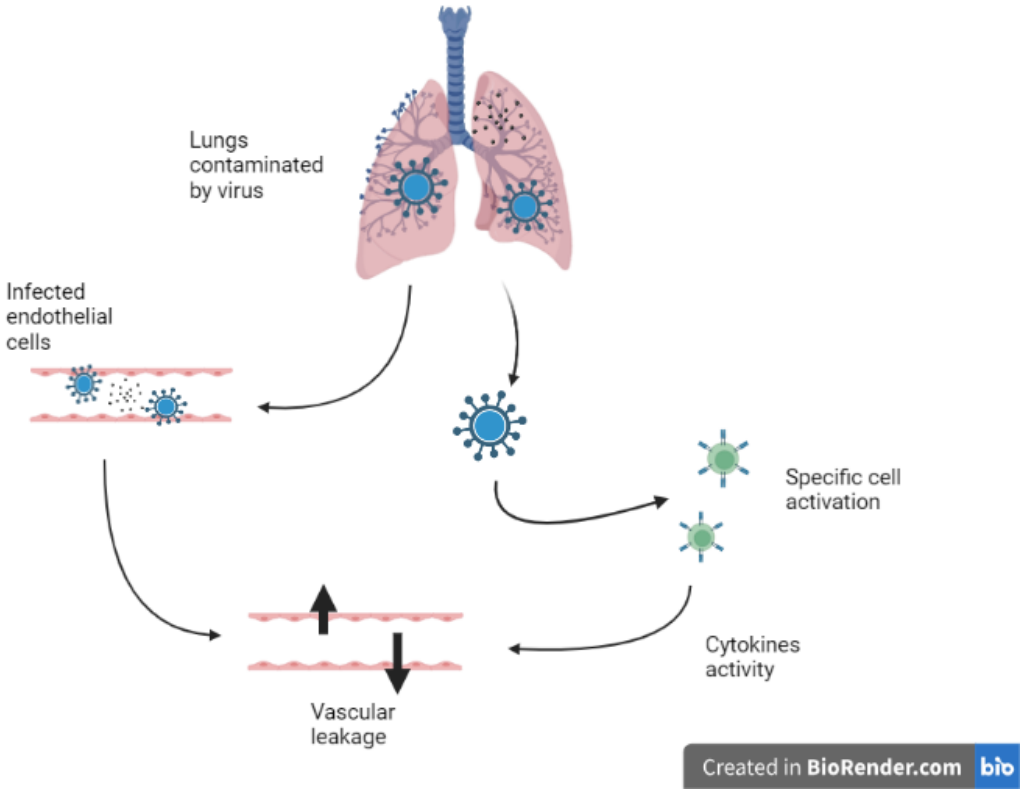

Fig. 2: Increased vascular permeability in response to virus infection.

of two to four weeks. There are commonly reports of lethargy and visual abnormalities (typically blurred vision). This febrile period may last from 3 to 7 days. Conjunctival hemorrhages and fine petechiae start to appear on the palate at the end of this period. A few hours to two days can pass during the hypotensive period. Majority deaths by HFRS are linked to severe irreversible shock at this stage and the severe cases can be characterized by hypotension and the patient even may go into shock quickly. This phase is characterized by thrombocytopenia, leucocytosis, and the beginning of severe hemorrhagic illness. Blood pressure returns to normal during the 3–7-day oliguric phase but kidney function temporarily deteriorates, causing azotaemia, oliguria, proteinuria, microscopic haematuria and even anuria. Patients with significant symptoms in oliguric phase, that is typically accompanied by stomach and back pain, need to have haemodialysis treatment. Elevated serum creatinine and urea levels are typical test results. Renal function begins to improve and urine output rises throughout the polyuric phase. The patient has a good prognosis when the diuretic phase starts. Patients can pass many litres of urine per day during this time, which can extend for days or weeks. It is challenging to distinguish between the five phases of HFRS in milder cases brought on by SEOV. Acute hemorrhagic symptoms and shock are uncommon in NE, but about one-third of patients have petechiae and other minor hemorrhagic symptoms. Instead of a full-blown shock episode, hypotension is detected. Overall, NE is frequently misdiagnosed because its clinical history is frequently atypical and more closely resembles a febrile sickness with stomach pain (Kanerva et al. 1998; Settergren 2000). A mild variant of HFRS brought on by an infection with SEOV has a clinical appearance and progression remarkably similar to HFRS brought on by HTNV. Though hepatitis is typically absent in other hantavirus infections, SEOV infections are frequently accompanied by it (Kim et al. 1995; Jonsson et al. 2008).

8. HANTAVIRUS CARDIOPULMONARY SYNDROME

HCPS is a more serious illness with fatality rates that range from 30 to 50 % compared to HFRS. Clinical symptoms of HCPS can range from mild hypoxemia to respiratory failure with cardiogenic shock, and the disease typically proceeds through three phases: prodromal, cardiopulmonary, and convalescent (Enria et al. 2001). Rapid development of bilateral infiltrates and coexistence of pleural effusion can result in respiratory failure and necessitates mechanical ventilation. Lactic acidosis, significant hemoconcentration and cardiogenic shock worsen this stage in more severe cases. Within hours of being hospitalized, patients can pass away. Patients that make it through the disease's initial phase enter the poly-uric stage that can be followed by the pulmonary oedema's remission. The recovery is typically full and without any aftereffects, despite the fact that the recovery is delayed, there are frequently complaints of weakness, exhaustion and poor exercise tolerance by the patients (Enria et al. 2001; Schönrich et al. 2008; Jonsson et al. 2010). Following this, cardiopulmonary phase quickly advances with sudden onset of a growing shortness of breath with cough and tachycardia. Hypotension and acute pulmonary oedema may also occur in the patients. Although lung and renal disease are typically attributed to HFRS and HCPS, respectively, growing medical understanding of clinical developments of HFRS and HCPS leads to the conclusion that the two conditions can overlap partially. In particular, there are increasingly more occurrences of HFRS with lung involvement and HCPS with renal and/or hemorrhagic involvement (Hughes et al. 1993; Kanerva et al. 1998; Linderholm and Elgh 2001).

9. DIAGNOSIS

Only a few cell lines have been used to effectively produce hantaviruses, with Vero E6 being the most popular. Virus isolation from humans or animals typically necessitates many steps. Before the viral

antigen is found in cells, it takes many weeks of blind transit. Therefore, in general clinical practice, isolation of virus is not employed for patient diagnosis but in epidemiological research to recover novel agents, it can be used. Haemagglutination inhibition test and the IFT are the major conventional immunological tests that are used to diagnose the HFRS. Enzyme-linked immunosorbent assay (ELISA) is also used to diagnose the HFRS. To detect the particular immunoglobulin the majority of regular laboratories currently use IFT. IFT can also be used IFT can also be used to detect the presence of specific antibodies in acute and the serum of recovering correspondents in the clinical diagnosis in establishing the diagnosis. Antibodies attain peak at the end of second week and can last up to 30 years, IFT detects these antibodies that start to manifest in the first week (Glass et al. 1991). The first serum sample had very high IgG titers titers in many patients of nephropathia epidemica (Niklasson et al. 1990). Only 50% of individuals with clinical nephropathia epidemica exhibit a fourfold raise in titer titer, according to IFT. If a particular IgG is present, it may indicate a past infection rather than the current state of the patient because in highly endemic parts of Sweden the prevalence rates of antibodies may exceed up to 30% in the older age groups (Niklasson et al. 1987). The patients of nephropathia epidemica have antibodies detectable by techniques like ELISA or NT or IFT lasting 20 to 50 years, as seen in KHF patients. Sero-epidemiology is therefore advantageous because lifelong exposure to the virus is shown by the existence of antibodies revealed by these sensitive assays. However, early IgG antibody detection, a lack of antibody titre ascent with high prevalence rates of antibodies can hinder accurate identification of patients. A g-capture IgM ELISA recently was created and tested (Jiang 1983). In first few days following the commencement of the disease, specific IgM was found and patients continued to be IgM positive for several months. With its excellent sensitivity and specificity, the IgM ELISA now is the most appropriate diagnostic test for patients. Two (Seoul and Hantaan virus) of three serologically different viruses that cause human disease, can only be distinguished by NT.

10. TREATMENT

The focus of care is on providing supportive treatment as there is currently no specific Food and Drug Administration-approved therapy for HFRS or even HCPS in the U.S. For close observation and clinical management, the patients with severe HFRS and HCPS are advised to be transferred to an intensive care unit. Maintaining fluid and electrolyte balance as well as circulatory volume is critical for anuric or leaky capillary patients and must be monitored very carefully for electrolyte balance, the function of kidneys and diuresis. Dialysis may be necessary for HFRS patients with significant renal failure, which is linked to pulmonary oedema and excessive fluid retention. Platelet transfusions may be done if there is significant bleeding and thrombocytopenia (Linderholm and Elgh 2001; Jonsson et al. 2010). In HCPS, it's important to regulate fluids, use pressors properly, and provide supplemental oxygen when necessary (Krüger et al. 2001). Ribavirin was successful in treating suckling mice infected with HTNV and was indicated to carry anti-hantaviral action (Huggins et al. 1986). Clinical investigations on HFRS patients from China has shown that at the beginning of symptoms if ribavirin is given in initial 5 days, it can significantly decrease the mortality rate dramatically (Huggins 1989; Huggins et al. 1991). In the treatment of HFRS in China, ribavirin has widely been used. It has been confirmed in a recent study by Rusnak et al. that giving IV ribavirin in early course of HFRS lessens the severity of renal insufficiency and the incidence of oliguria (Rusnak et al. 2009). Ribavirin given intravenously has also been investigated for the treatment of HCPS. However, ribavirin medication provided no therapeutic effect for the patients in a few small trials (Chapman et al. 1999; Mertz et al. 2004).

11. PREVENTION

The main source of Seoul virus are the wild rats. A chance could be present that rats migrating via, say, international shipping could transmit this human illness around the world. In addition to attempting to

reduce this risk, the prevention of HFRS disease now rests on evading the recognized endemic habitat and decreasing the exposure to rats and their excrement. Expeditions to eradicate rodents can prove to be very costly and challenging but they have occasionally been successful (Yanagihara and Gajdusek 2019). An effective and intact vaccination has received first preference in HFRS research because of the illness's severity and some regions' high occurrence rates. Trials using an inactivated vaccine based on the Hantaan virus that was created in accordance with the Japanese encephalitis vaccine protocol are now being done (Lee et al. 1991). Animals that had received vaccinations were protected from Hantaan virus infection. The vaccines contain antigens of Hantaan virus and were produced in recombinant vaccinia virus (Schmaljohn et al. 1990). Nevertheless, the scarcity of appropriate animal models hinders the development of vaccines against all hantaviruses, regardless of vaccination method. The most pressing issues that need to be addressed right now are firstly the therapeutic interventions to be made in patients with severe shock and life-threatening hemorrhagic cases. Secondly the arbitration of entire clinical spectrum of infections. Furthermore, issue of the consequences like CVS and renal damage as well as the creation and production of a reliable vaccine.

REFERENCES

Ahlm C et al., 2000. Serologic evidence of Puumala virus infection in wild moose in northern Sweden. The American Journal of Tropical Medicine and Hygiene 62: 106-111.

Ala-Houhala I et al., 2002. Increased glomerular permeability in patients with nephropathia epidemica caused by Puumala hantavirus. Nephrology Dialysis Transplantation 17: 246-252.

Baek LJ et al., 1988. Leakey virus: a new hantavirus isolated from Mus musculus in the United States. Journal of General Virology 69: 3129-3132.

Bishop D et al., 1980. Bunyaviridae. Intervirology 14: 125-143.

Brummer-Korvenkontio M et al., 1980. Nephropathia epidemica: detection of antigen in bank voles and serologic diagnosis of human infection. Journal of Infectious Diseases 141: 131-134.

Chapman LE et al., 1999. Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. Antiviral Therapy 4: 211-219.

Chen L and Yang W, 1990. Abnormalities of T cell immunoregulation in hemorrhagic fever with renal syndrome. Journal of Infectious Diseases 161: 1016-1019.

Enria D et al., 2001. Clinical manifestations of New World hantaviruses. Hantaviruses 2001: 117-134.

Ferrer C et al., 2007. Genetic susceptibility to Andes Hantavirus: Association between severity of disease and HLA alíeles in Chilean patients. Revista Chilena de Infectologia: Organo Oficial de la Sociedad Chilena de Infectologia 24: 351-359.

Gavrilovskaya IN et al., 1999. Cellular entry of hantaviruses which cause hemorrhagic fever with renal syndrome is mediated by β3 integrins. Journal of Virology 73: 3951-3959.

Glass G et al., 1991. Association of chronic renal disease, hypertension, and infection with a rat-borne hantavirus. In: Calisher CH, editor. Hemorrhagic fever with renal syndrome, tick-and mosquito-borne viruses; pp: 69-80.

Groeneveld PH et al., 1995. Increased production of nitric oxide in patients infected with the European variant of hantavirus. Scandinavian Journal of Infectious Diseases 27: 453-456.

Heyman P et al., 2009. Hantavirus infections in Europe: from virus carriers to a major public-health problem. Expert Review of Anti-infective Therapy 7: 205-217.

Huggins JW, 1989. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. Reviews of Infectious Diseases 11: S750-S761.

Huggins JW et al., 1991. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. Journal of Infectious Diseases 164: 1119-1127.

Huggins JW et al., 1986. Ribavirin therapy for Hantaan virus infection in suckling mice. Journal of Infectious Diseases 153: 489-497.

Hughes JM et al., 1993. Hantavirus pulmonary syndrome: an emerging infectious disease. Science 262: 850-851.

Jiang YT, 1983. A preliminary report on hemorrhagic fever with renal syndrome in China. Chinese Medical Journal 96: 265-268.

Jonsson CB et al., 2010. A global perspective on hantavirus ecology, epidemiology, and disease. Clinical Microbiology Reviews 23: 412-441.

Jonsson CB et al., 2008. Treatment of hantavirus pulmonary syndrome. Antiviral Research 78: 162-169.

Kanerva M et al., 1998. Pathogenesis of Puumala and other hantavirus infections. Reviews in Medical Virology 8: 67-86.

Khaiboullina SF et al., 2005. Hantaviruses: molecular biology, evolution and pathogenesis. Current Molecular Medicine 5: 773-790.

Kilpatrick ED et al., 2004. Role of specific CD8+ T cells in the severity of a fulminant zoonotic viral hemorrhagic fever, hantavirus pulmonary syndrome. The Journal of Immunology 172: 3297-3304.

Kim YS et al., 1995. Hemorrhagic fever with renal syndrome caused by the Seoul virus. Nephron 71: 419-427.

Klempa B, 2009. Hantaviruses and climate change. Clinical Microbiology and Infection 15: 518-523.

Korva M et al., 2011. HLA-associated hemorrhagic fever with renal syndrome disease progression in Slovenian patients. Clinical and Vaccine Immunology 18: 1435-1440.

Krüger DH et al., 2001. Hantavirus infections and their prevention. Microbes and Infection 3: 1129-1144.

Leduc JW et al., 1986. Global survey of antibody to Hantaan-related viruses among peridomestic rodents. Bulletin of the world Health Organization 64: 139.

Lee HW, 1982. Hemorrhagic fever with renal syndrome (HFRS). Scand. J. Infect. Dis. Suppl 36: 82-85.

Lee HW et al., 1991. Field trial of an inactivated vaccine against hemorrhagic fever with renal syndrome in humans. In: Calisher CH, editor. Hemorrhagic Fever with Renal Syndrome, Tick-and Mosquito-Borne Viruses; pp: 35-47.

Lee HW et al., 1978. Isolation of the etiologic agent of Korean hemorrhagic fever. Journal of Infectious Diseases 137: 298-308.

Linderholm M and Elgh F, 2001. Clinical characteristics of hantavirus infections on the Eurasian continent. Hantaviruses 2001: 135-151.

Linderholm M et al., 1997. Impaired pulmonary function in patients with hemorrhagic fever with renal syndrome. Clinical Infectious Diseases 25: 1084-1089.

Mackow E and Gavrilovskaya I, 2001. Cellular receptors and hantavirus pathogenesis. Hantaviruses 2001: 91-115.

MacNeil A et al., 2011. Hantavirus pulmonary syndrome. Virus Research 162: 138-147.

Mäkelä S et al., 2002. Human leukocyte antigen–B8-DR3 is a more important risk factor for severe puumala hantavirus infection than the tumor necrosis factor–α (− 308) G/A polymorphism. The Journal of Infectious Diseases 186: 843-846.

Mertz GJ et al., 2004. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. Clinical Infectious Diseases 39: 1307-1313.

Nichol ST et al., 1993. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 262: 914-917.

Niklasson B and Le Duc J, 1984. Isolation of the nephropathia epidemica agent in Sweden. The Lancet 323: 1012-1013.

Niklasson B et al., 1987. Nephropathia epidemica: incidence of clinical cases and antibody prevalence in an endemic area of Sweden. Epidemiology & Infection 99: 559-562.

Niklasson B et al., 1990. Haemorrhagic fever with renal syndrome: evaluation of ELISA for detection of Puumala-virus-specific IgG and IgM. Research in Virology 141: 637-648.

Niklasson D and LeDuc JW, 1987. Epidemiology of nephropathia epidemica in Sweden. Journal of Infectious Diseases 155: 269-276.

Peebles RS and Graham BS, 2001. Viruses, dendritic cells and the lung. Respiratory Research 2: 1-5.

Plyusnin A and Morzunov S, 2001. Virus evolution and genetic diversity of hantaviruses and their rodent hosts. Hantaviruses 2001: 47-75.

Rusnak JM et al., 2009. Experience with intravenous ribavirin in the treatment of hemorrhagic fever with renal syndrome in Korea. Antiviral Research 81: 68-76.

Sadeghi M et al., 2011. Cytokine expression during early and late phase of acute Puumala hantavirus infection. BMC Immunology 12: 1-10.

Saksida A et al., 2011. Serum levels of inflammatory and regulatory cytokines in patients with hemorrhagic fever with renal syndrome. BMC Infectious Diseases 11: 1-8.

Schmaljohn CS et al., 1990. Antigenic subunits of Hantaan virus expressed by baculovirus and vaccinia virus recombinants. Journal of Virology 64: 3162-3170.

Schönrich G et al., 2008. Hantavirus-induced immunity in rodent reservoirs and humans. Immunological Reviews 225: 163-189.

Settergren B, 2000. Clinical aspects of nephropathia epidemica (Puumala virus infection) in Europe: a review. Scandinavian Journal of Infectious Diseases 32: 125-132.

Settergren B et al., 1990. Glomerular filtration rate and tubular involvement during acute disease and convalescence in patients with nephropathia epidemica. Journal of Infectious Diseases 161: 716-720.

Song G et al., 1984. Antigenic difference between viral strains causing classical and mild types of epidemic hemorrhagic fever with renal syndrome in China. Journal of Infectious Diseases 150: 889-894.

Temonen M et al., 1996. Cytokines, adhesion molecules, and cellular infiltration in nephropathia epidemica kidneys: an immunohistochemical study. Clinical Immunology and Immunopathology 78: 47-55.

Terajima M et al., 1999. High levels of viremia in patients with the Hantavirus pulmonary syndrome. Journal of Infectious Diseases 180: 2030-2034.

Vaheri A et al., 2013. Hantavirus infections in Europe and their impact on public health. Reviews in Medical Virology 23: 35-49.

Vapalahti O et al., 2003. Hantavirus infections in Europe. The Lancet Infectious Diseases 3: 653-661.

Yanagihara R and Gajdusek D, 2019. Hemorrhagic fever with renal syndrome: a historical perspective and review of recent advances. CRC Handbook of Viral and Rickettsial Hemorrhagic Fevers 2019: 155-182